Paid Circulation, 26,197

The New England Journal of Medicine

FORMERLY THE BOSTON MEDICAL AND SURGICAL JOURNAL — *Established 1828*

VOLUME 248 · FEBRUARY 12, 1953 · NUMBER 7

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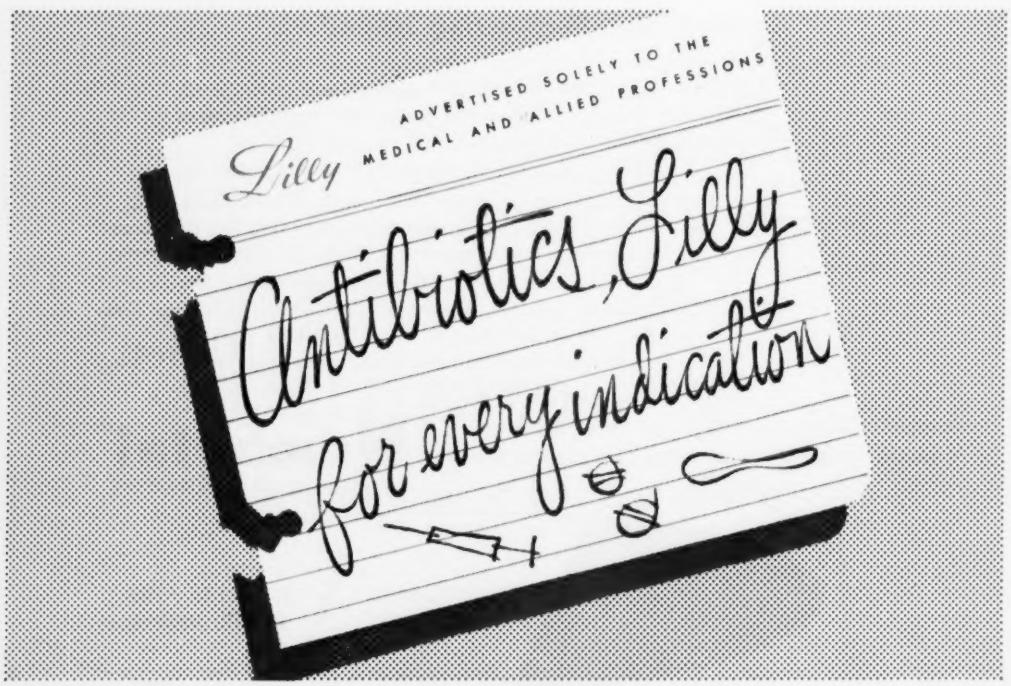
Entered as second-class matter, November 16, 1932, at the post office at Boston, Massachusetts, under the Act of March 3, 1879.
Published weekly at 8 Fenway, Boston 15. Domestic, $8.00 per year.



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The New England
Journal of Medicine

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Volume 248 FEBRUARY 12, 1953 Number 7

EPIDEMIC PLEURODYNIA IN TEXAS*
A Study of 22 Cases

ROBERT J. HUEBNER, M.D.,† JOE A. RISSER, M.D., JOSEPH A. BELL, M.D.,‡ EDWARD A. BEEMAN, M.D.,§ PAUL M. BEIGELMAN, M.D.,¶ AND JAMES C. STRONG, M.D.||

BETHESDA, MARYLAND

EPIDEMIC pleurodynia (Bornholm disease, epidemic myalgia, devil's grippe), first described by Daae[1] and Homann[2] in Norway in 1872 and by Finsen[3] in Iceland in 1874, has been reported with ever-increasing frequency since the appearance of the classic monograph by Sylvest[4] in 1933. Although a virus etiology was postulated by many observers, attempts to isolate an infectious agent of likely etiologic significance were unsuccessful until recently.

In 1949 Curnen, Shaw and Melnick,[5] reporting the occurrence of the Connecticut 5 Coxsackie virus (classified by Dalldorf as B1) in patients with diagnoses of nonparalytic poliomyelitis or aseptic meningitis, noted the recovery of the virus from a patient ill with signs and symptoms of epidemic pleurodynia. Subsequently, pleurodynia-like illnesses occurred in laboratory personnel working with this virus,[6] and Weller et al.[7] demonstrated several strains antigenically similar to the Connecticut 5 virus in throat washings collected during an epidemic of pleurodynia in Boston in 1947.[8] Immune responses during these infections led to the hypothesis that the Connecticut 5 virus represents an etiologic agent for this widespread disease.

A report by Lazarus and his associates[9] of the recovery of another type of B virus, classified as B3 by Dalldorf, in cases of epidemic pleurodynia occurring during 1950 in the State of Washington indicated that different immunologic types of Group B viruses might be capable of causing pleurodynia in a manner analogous to the causation of herpangina[10] by different immunologic members of the Group A Coxsackie viruses. On the other hand, the studies of Findlay and Howard[11] implicated a Group A virus (Dalldorf's Type A2)[12] as a causative agent of epidemic pleurodynia in England — a virus implicated repeatedly as a cause of herpangina in the United States. However, Findlay and Howard demonstrated a serologic relation between their Type A2 virus and an unidentified Connecticut strain received from Melnick. This was inconsistent with reports from other laboratories and suggested the possibility that the Connecticut 5 virus was present as an unrecognized contaminant in the material derived from the patients. Such a possibility is compatible with other reports describing the simultaneous occurrence of multiple Coxsackie viruses in single cases[13] and with data that will be presented in this article.

Although the evidence suggesting a causal relation between certain Group B viruses and epidemic pleurodynia appears to be stronger than that linking these viruses with poliomyelitis,[14] aseptic meningitis[14] or poliomyelitis-like illness,[15, 16] the available published data supporting this hypothesis are based almost exclusively on the study of sick persons. Therefore, it seemed to us that it would be desirable to perform studies of epidemic pleurodynia in which observations during outbreaks of specific illnesses were controlled by simultaneous observations of sick persons and equivalent groups of healthy persons in the same community.

An opportunity to carry out such studies was provided during the latter part of the summer of 1951, when state health authorities** brought to the attention of the Laboratory of Infectious Diseases of the National Microbiological Institute an outbreak of epidemic pleurodynia in northeastern Texas that had been recognized by local physicians. Collaborative studies were carried out by representatives of the Texas State Health Department, and the Laboratory of Infectious Diseases, with the assistance of practicing physicians in the epidemic

*From the Federal Security Agency, Public Health Service, National Institutes of Health, National Microbiological Institute, Laboratory of Infectious Diseases.

†Senior surgeon and chief, Virus and Rickettsial Section, Laboratory of Infectious Diseases, National Microbiological Institute.

‡Medical director and chief, Section on Epidemiology, Laboratory of Infectious Diseases, National Microbiological Institute.

§Senior assistant surgeon, Virus and Rickettsial Section, Laboratory of Infectious Diseases, National Microbiological Institute.

¶Senior assistant surgeon, Epidemiology Section, Laboratory of Infectious Diseases, National Microbiological Institute.

||Assistant director, Department of Public Health, City of Dallas, Dallas, Texas; formerly, director, Paris-Lamar County Health Unit, Paris, Texas.

**Dr. J. V. Irons, director of laboratories, Texas State Department of Health, and Dr. George W. Cox, state health officer, State Department of Health, Austin, Texas.

area.* An epidemiologic study of a small community embracing the area of Telephone, Texas, will be reported later; it includes more than 700 persons, approximately 65 of whom gave clinical evidence of concurrent illness or histories suggestive of recent attacks of pleurodynia. The present paper reports the isolation of viruses (Dalldorf's B3 and A1) in suckling mice from the stools of 18 of 22 persons ill with the clinical diagnosis of epidemic pleurodynia. Furthermore, these data pointedly emphasize some of the difficulties inherent in attempts to deduce etiologic significance from the mere isolation of Coxsackie viruses with or without a subsequent rise in antibody levels.

Materials and Methods

Virus Isolation

Fecal specimens were collected from each of the patients as soon as they were brought under study. Such specimens were collected in sterile 4-ounce ointment jars, were frozen on solid carbon dioxide and shipped via air express to the National Institutes of Health, Bethesda, Maryland. Except for a few minor modifications, the methods used for isolation and identification of the virus were essentially the same as those previously described in detail.[17] Antibiotics instead of ether were used to eliminate bacterial contaminants from the original specimens, and for primary isolation attempts mice one day old were used instead of mice three days old, since the former represent more sensitive laboratory hosts for the Group B viruses. In mice infected with Group B virus the clinical signs of illness most frequently observed were extreme weakness, ataxia, spasticity or paralysis of extremities. Brain as well as muscle was harvested from animals showing such signs, and both tissues were incorporated into a suspension for further serial passage in infant mice.

Viruses established in subsequent passages were identified immunologically by means of a neutralization test previously described in detail.[17] The agents belonging to the A group were also typed in the complement-fixation test.[17, 18] By methods previously described[18] it was possible to identify multiple immunologic types of virus occurring simultaneously in some of the fecal specimens.

Serologic Studies of Patients

Acute and convalescent serums from patients with pleurodynia were examined for the development of neutralizing and complement-fixing antibodies against the prototype viruses isolated in the Texas study area and against certain other A and B strains, which were included as controls. In confirmation of Melnick's earlier reports,[15, 19] we found that the serial dilution of serum tested with a fixed quantity of virus gave a somewhat more sensitive measurement of the development of neutralizing antibodies against the Group B viruses than the virus-dilution technic previously used in this laboratory for testing antibody responses to Group A virus infections.[17] Serial twofold dilutions of serum, 1:20 to 1:640 (final dilution), were mixed with a dose of virus calculated to give 100 LD_{50}'s per 0.04 cc. of mixture. The mixtures were each inoculated intraperitoneally into 1 or 2 litters of mice (0.04 cc. per mouse). The serial twofold dilution nearest to the theoretically calculated dilution, which protected at least 50 per cent of the mice (Reed–Muench method), was considered as the titer of the serum.

The complement-fixation test[20] was also used in the determination of serum antibody response of sick persons. The limitations of the complement-fixation procedure for demonstrating antibodies against Coxsackie viruses in human serums has been described in detailed reports.[20, 21]

Clinical Features

The outbreak will be discussed in the later report of epidemiologic findings. In brief, typical cases of epidemic pleurodynia consistent with features discussed below and with clinical descriptions of others[5-7] occurred in the vicinity of Bonham, Fannin County, Texas (from late June to September, 1951). The pattern of the outbreak was similar to those described in rural areas by Sylvest[4] and Pickles.[22] Multiple cases occurred in certain families, as many as 3 or 4 persons becoming ill almost simultaneously or in quick succession with intervals of three to five days between cases.

Sylvest[4] stated that chest or abdominal pain, often paroxysmal and aggravated by respiration, was the most distinctive characteristic of this disease. Fever was also a constant finding. Headache was frequent. The prognosis was invariably good, and the outbreaks occurred in the summer. Pickles,[22] describing similar though less extensive rural outbreaks, made almost identical observations. He further emphasized the rarity of vomiting, cough or pharyngeal inflammation. As described by Sylvest,[4] complications of pleurodynia are uncommon, but include orchitis, pleurisy, and rarely meningitis.

Similar clinical features have been described in urban outbreaks.[8] Some of the conditions with which pleurodynia may be confused are appendicitis, common-bile-duct obstruction, acute cholecystitis, pancreatitis, perforated peptic ulcer, coronary insufficiency, pneumonia, pleurisy, pulmonary infarction, intestinal infections and occasionally the pre-eruptive phase of herpes zoster.

Characteristically, patients in this study had acute onset of fever, headache and anorexia, accompanied by severe, paroxysmal abdominal or chest pain aggravated by respiration. Sore throat, nausea and vomiting were uncommon complaints.

The sensation of difficult breathing was particularly striking. Descriptions by patients were stereo-

*Drs. J. M. Donaldson, L. C. Biggers, L. Morgan, J. L. Stevens, and E. C. Williams from Bonham, Texas.

typed and vivid: "I can't breathe," "pain cut off my breath," "can't get a real long breath" and "it hurts to breathe." A definite diagnosis of the entity was dependent on the presence of this respiratory component. Recovery was often interrupted by recurrences of pain and fever. Depending on the number of recurrences, the total duration of illness varied from one to twenty days. Sequelae were not common, but persistent and painful orchitis developed in several patients. A number of patients described, but were unable to demonstrate, localized, tender muscle swellings of the abdomen occurring at the height of illness. Local inhabitants succinctly termed these "pones." Similar lesions have been described by Sylvest.[4] There was little evidence of central-nervous-system involvement except for cloudy sensoriums in several severely ill patients. Spinal-fluid studies performed in a few cases were negative. Paralytic poliomyelitis was not encountered in the entire study area during the outbreak. In only 1 case was a diagnosis of nonparalytic poliomyelitis tentatively and briefly considered by the attending physicians.

A typical family outbreak occurred as follows:

Case 4. E. J. McC., a 14-year-old schoolgirl, was suddenly stricken, on the morning of August 10, 1951, with a severe pain in the left lower portion of the chest and epigastrium that was aggravated by respiration, talking or sneezing. The pain completely subsided within an hour, and the patient apparently felt quite well. Similar acute severe pain affecting the lower left rib cage and upper abdomen recurred late that afternoon, and she was hospitalized at 4 p.m. The temperature was 99.9°F., and the only positive physical finding was muscle guarding over the left upper quadrant of the abdomen. Blood and urinary findings were within normal limits. During the first night, anorexia was present and there were 5 episodes of pain lasting 5 to 30 minutes, none of which required therapy. The patient complained only of fatigue, but ate well the next day. A brief episode of pain low in the anterior portion of the chest occurred on the 3d day, but subsided rapidly. She was discharged on the following day.

Case 5. M. B. McC., the 16-year-old sister of the patient in Case 4, suffered a sudden severe pain in the right lower quadrant of the abdomen, fever and mild nausea at 2 p.m. on August 10, 1951. Breathing, talking and movement intensified the pain. She was hospitalized in the same hour as her sister. Physical findings included rapid, shallow respiration, a temperature of 101.6°F., a pulse rate of 120, reddening of the faucial pillars and muscle guarding and numbness over the area of abdominal pain. Blood and urinary findings were within normal limits. Demerol and oxygen therapy induced prompt remission of the pain, but the temperature quickly rose to 104°F., accompanied by clouding of the sensorium, and this was followed by defervescence and general improvement 6 hours later. Successively milder and shorter episodes of fever and pain localized to the lower rib margin and epigastrium recurred on the following afternoon and on the morning of the 3d hospital day. She was discharged on the following day, but was asthenic and complained of poor memory and anorexia for 3 weeks.

Case 6. L.McC., the 6-year-old brother of the patients in Cases 4 and 5, suddenly experienced severe upper abdominal pain, intensified with each breath, on the morning of August 12, 1951, and was immediately hospitalized. The temperature on admission was 101.8°F., respiration was shallow, and the upper abdomen was sore and tense. Examinations of blood and urine revealed no abnormalities. Pain subsided after administration of Demerol and oxygen, but the temperature rose to 103.6°F.; and the pulse to 122; the respirations were 30. Twelve hours later, he was afebrile. An episode of severe abdominal pain and fever recurred the next afternoon, persisting for 2½ hours. He was discharged on the 3d hospital day. Typical chest pain recurred twice thereafter, once on August 20 and again on August 22. Asthenia and anorexia persisted for 2 more weeks.

Sources and Selection of Patients for Virus Studies

The 22 cases of epidemic pleurodynia included in this report were selected from among patients referred by practicing physicians in Fannin County, Texas, and some of the nearby areas.* The patients include only those who were observed by us during an illness characterized by fever and sudden onset of acute pain in the chest aggravated by breathing, and on whom specimens were obtained during illness. Five patients fulfilling these criteria had other medical or surgical conditions that in themselves might have been responsible for the symptoms. Thus, the 22 cases finally selected for study do not necessarily represent a cross-section of all persons ill with pleurodynia-like illness or reflect accurately the various clinical syndromes possibly produced by this disease.

Results

Stool specimens from 18 of 22 patients studied yielded Coxsackie viruses (Table 1). The first agents to be recognized and typed by immunologic methods were strains of Dalldorf's Group A, Type 1. This type, which was found in several initial specimens, produces in primary passage unique and rather easily recognized overt signs of paralysis in mice that differ on a clinical basis from those produced by other A types and members of Group B.[17]

Further observations of other specimens, however, revealed that it was not this virus but another agent lethal for suckling mice that was present in the stools of most of the patients. This second virus, classified by Dalldorf as B3,† reported previously by Melnick†[19, 26] and Lazarus,†[9] was more apparent in one-day-old mice than in three-day-old mice. On primary and early passages, it propagated slowly and irregularly, producing almost none of the signs in the suckling mouse characteristic of the Group A strains. Ataxia, tremors, spasticity and weakness occurring between the third and the twelfth post-injection day were the only signs prior to death. Indeed, such manifestations were difficult to distinguish from frequent undetermined causes of infant-mouse mortality. However, on subsequent passages more regular production of ataxia and tremors at expected intervals, followed by 100 per cent mortality, established clearly the presence of an agent that was identified subsequently in each instance by reciprocal cross-neutralization tests as similar to or identical with the B3 virus.

Table 1 summarizes clinical and virus-isolation data on the 22 patients. Stool specimens from 16

*Dr. J. M. Donaldson, Fannin County health officer, Bonham, Texas, and Drs. L. Morgan, J. L. Stevens and E. C. Williams, from the Medical and Surgical Clinic, Bonham, Texas.

†We are indebted to Drs. G. Dalldorf, J. L. Melnick and A. S. Lazarus for providing us with their prototypes of this strain.

patients yielded the B3 virus. Only 1 (Case 20, Table 1), an infant, had in addition a complicating illness suggestive of another entity. Several days after her initial episode had subsided, fever recurred, and was followed on the third day by a maculopapular generalized rash suggestive of roseola infantum. From this patient two viruses, B3 and A1, were recovered. Two patients experienced prolonged sequelae. In Case 2 pain and swelling of the left testis developed seven days after the onset of typical illness. This was accompanied by an exacerbation of fever lasting several days, and the ing towns and in Fort Worth. In each circumstance they were exposed to children with febrile illnesses. A. D. became ill with a fever during a subsequent visit to Denison, Texas. Her chief complaint was headache. She did not have chest or abdominal pain. Her physician and her mother noted "ulcers in her throat." Although she did not have the classic symptoms of chest and abdominal pain, she was included as a probable case because of the typical syndromes observed previously in her brothers. From the standpoint of her clinical history a more tenable diagnosis would have been her-

TABLE 1. *Results of Attempts to Isolate Coxsackie Viruses from the Stools of 22 Patients with Clinical Diagnoses of Epidemic Pleurodynia.*

CASE NO.	PATIENT*	SEX	AGE	DATE OF ONSET	TOTAL DURATION	FEVER AND PAIN IN CHEST†	EPIGASTRIC PAIN	LOWER ABDOMINAL PAIN
			yr.		*days*			
1	J. D.	M	9	8/1	4	+	—	—
2	W. D.	M	14	8/4	20	+	—	—
3	A. D.	F	8	8/5	8	Fever (no pain)	—	—
4	E. J. McC.	F	14	8/10	4	+	+	—
5	M. B. McC.	F	16	8/10	7	+	—	+
6	L. McC.	M	6	8/12	5	+	+	—
7	J. R. M.	M	17	8/13	3	+	+	+
8	L. M.	F	5	8/18	1	+	—	—
9	R. M.	M	21	8/20	4	+	—	+
10	B. T.	M	3	8/18	4	+	—	+
11	A. T.	M	26	8/21	12	+	—	—
12	E. F.	F	32	8/18	4	+		—
13	J. R. D.	M	18	8/18	7	+	+	+
14	E. E. C.	F	56	8/16	6	+	+	—
15	P. H.	M	84	8/17	5	+	—	—
16	E. J.	F	72	8/15	4	+	+	—
17	R. C. F.	M	23	8/21	5	+	—	—
18	I. R.	F	67	8/23	7	+	—	—
19	J. F.	M	9	8/23	2	+	—	—
20	M. C.	F	1	8/23	9	+	—	+
21	F. H.	F	10	8/28	5	+	—	—
22	E. P. B.	F	35	8/30	7	+	+	—

*Grouping of names indicates members of the same household.

†Fever and chest pain provided the clinical basis for selection of cases.

‡B3 (Dalldorf[20]) = "Nancy" (Melnick[19]) strain. A1 (Dal ldorf[12]) = Easton 2 and NIH 138 (Melnick[23] and Huebner[19]) strains.

orchitis was evident on physical examination seventeen days after onset. There was no clinical evidence of mumps. J. R. D. (Case 13) had a recurrence of fever and chest pain a month after the initial attack. J. D. (Case 1) had been hospitalized in a nearby city, where because his neck seemed stiff, abortive poliomyelitis was briefly considered in differential diagnosis. Unfortunately, spinal-fluid studies were not performed.

Four patients had Group A, Type 1, virus in their stools. Two of these also harbored the B3 virus. A. D. (Case 3), from whom only Group A, Type 1, was recovered, was seen by us shortly after her illness and in retrospect does not appear to have had pleurodynia, although her 2 brothers, J.D. and W.D., were observed during typical attacks of pleurodynia. A few days before the three illnesses began, this family had visited relatives in neighbor-

pangina. E. E. C. (Case 14), a fifty-six-year-old woman, was found to be harboring only Group A, Type 1, virus on August 17. She had been hospitalized with a fracture of the tibia on August 8; eight days after admission and four days after exposure within the same hospital ward to 3 typical cases (Cases 4, 5 and 6, discussed above) she awakened from a sound sleep with a severe pain in the left lower part of the thorax that required morphine for relief. Although her clinical course was in all respects suggestive of epidemic pleurodynia a pulmonary embolus could not be ruled out and must be considered as another possible source of the pain. The temperature did not exceed 100.4°F. during the initial episode or during the succeeding two days, which were marked by recurrences of chest pain. The fact that neutralizing antibodies against the B3 virus failed to develop suggests

that the failure to isolate this virus was not due to technical inadequacies (Table 2).

The presence of Group A, Type 1, virus in 2 patients (Cases 4 and 20) also harboring Group B, Type 3, virus was associated with no manifestations other than those observed in other cases of pleurodynia yielding only Group B, Type 3, virus. The probable occurrence of roseola infantum after a typical episode of pleurodynia in Case 20 could hardly be attributed to either Group A or Group B viruses since we have failed in several attempts under favorable circumstances to recover such acute attack her subsequent course must be regarded as atypical.

Throat washings were obtained on approximately the same day as stool specimens from 15 of the 22 patients. Two of these specimens yielded virus — those from R. C. F. (Case 17) and from J. R. M. (Case 7). Both strains recovered from throat washings were identical with the B3 strain.

Serologic Studies

Serum specimens taken near onset and in convalescence were available on 14 of the 22 patients.

TABLE 1 (*Concluded*).

Case No.	Headache	Other Signs or Symptoms	Sequelae	Concurrent or Complicating Illnesses	Date Stool Collected	Types of Coxsackie Virus Isolated‡	
1	+	Stiff neck			8/21	B3	
2	—	Anorexia	Orchitis		8/21	B3	
3	+	Ulcers in throat			8/21		A1
4	—				8/17	B3	A1
5	+	Cloudy sensorium			8/17	B3	
6	+				8/17	B3	
7	+	Anorexia			8/21	B3	
8	—				8/21	B3	
9	+	Anorexia			8/21	B3	
10	—	Sore throat, nausea and vomiting			8/23	B3	
11	+				8/23	B3	
12	—				8/22	B3	
13	+	Sore throat	Recurrence of fever and pain 1 mo. later		8/24	B3	
14	+			Fracture of tibia	8/17		A1
15	—			Coronary-artery disease	8/21	None	
16	—			Coronary-artery disease and diabetes	8/17	None	
17	+				8/25	B3	
18	+				8/25	None	
19	—				8/23	B3	
20	—			Roseola infantum	8/24	B3	A1
21	—				8/29	B3	
22	+	Mucoid diarrhea and griping abdominal pain for 10 days			9/1	None	

agents from infants with that disease[10] in another area.

No viruses were recovered from 4 patients, and neutralization tests performed on acute and convalescent serums from 3 of these revealed a complete absence of antibodies against the B3 virus (Table 2). Two of these patients (Cases 15 and 16) had previous hospital admissions with diagnoses of recurrent myocardial infarction. Since no electrocardiographic changes were observed epidemic pleurodynia was considered as a more probable clinical diagnosis. E. P. B. (Case 22), a thirty-five-year-old woman, suffered from a mucoid diarrhea and griping abdominal pain for ten days after an attack of fever and pain in the epigastrium and lower thorax. Although the clinical diagnosis of pleurodynia seemed inescapable during the initial

The results of neutralization and complement-fixation tests performed to date on these specimens are shown in Table 2. A rise in neutralizing antibody levels against B3 virus was demonstrated in the serums of 7 persons from whom B3 virus was isolated. One patient (E. McC.) from whom B3 virus was recovered showed a high titer in the initial serum taken seven days after onset, and a specimen taken one month later revealed the same high titer. Five patients not only showed no rise in neutralizing antibodies against B3 virus but also did not give evidence of any neutralizing antibodies. Since virus was not recovered from 4 of these patients, this was not unexpected. However, E. F. (Case 12) had a typical case of pleurodynia, and B3 virus was found in the stool on repeated examination. The failure to demonstrate neutralizing antibodies in serum taken three or four weeks after

onset in a person harboring virus is a unique experience in our extensive immunologic studies of persons infected with Coxsackie viruses. Melnick, however, reported delayed antibody responses in several persons infected with the Ohio 1 virus. However, a serum taken from the same patient more than two months after onset still revealed no neutralizing antibodies.

Cases 4 and 14, infected with strain A1, exhibited significant serum antibody rises to this strain, as did Case 19, from whom this virus was not recovered. Neutralization tests against strain A4 (High Point), occurrence of similar elevations against other strains of Coxsackie viruses, however, renders interpretation difficult, and at the present time the complement-fixation test must be regarded as an unreliable indication of previous human infection with these viruses.

Discussion

Physicians practicing in sparsely populated rural communities are frequently afforded the opportunity to make astute observations on the clinical and epidemiologic characteristics of infectious dis-

Table 2. *Serum Antibody Responses Demonstrated in the Neutralization and Complement-Fixation Test.*

Case No.	Patient	Date of Onset	Date of Blood Specimen	Strain B3*		Strain A1†		Strain A4‡		Virus Isolated
				Neutralization-serum titer	Complement-fixation test	Neutralization-serum titer	Complement-fixation test	Neutralization-serum titer	Complement-fixation test	
4	E. McC.	8/10	8/17	320	<64	<20	0	—	0	B3 and A1
			9/10	320	>64	640	32	—	0	
5	M. McC.	8/10	8/17	40	—	80		<20		B3
			9/10	320	32	160		<20		
6	L. McC.	8/12	8/17	80	0	—	0	<20	0	B3
			9/10	640	32	—	0	<20	0	
7	J. R. M.	8/13	8/21	+§	16	<20	0	—	0	B3
			9/5	+	64	<20	8	—	0	
9	R. M.	8/20	8/21	<20	8	20	0	20	0	B3
			9/6	—	—			—	—	
			9/20	160	64	20	0	20	0	
11	A. T.	8/21	8/23	<20	0	—	16	40	8	B3
			9/20	>640	16	—	16	80	8	
12	E. F.	8/18	8/22	<20	8	+§	8	—	0	B3
			9/10	<20	16	+	8	—	0	
			4/16/52	<20						
13	J. R. D.	8/18	8/23	80	0	80	0	<20	0	B3
			9/18	320	16	40	0	<20	0	
14	E. E. C.	8/16	8/17	<20	0	160	0	—	0	A1
			9/27	<20	0	>640	0	—	0	
15	P. H.	8/17	8/21	<20	0					None
			9/5	<20	0					
16	E. J.	8/15	8/17	<20	64					None
			9/20	<20	64					
17	R. C. F.	8/21	8/25	<20	16	<20	0	40	0	B3
			9/15	640	64	<20	0	80	>16	
19	J. F.	8/23	8/23	<20	0	40	0	—	8	B3
			9/19	>640	16	320	0	—	8	
22	E. P. B.	8/30	9/1	20	16	20	0			None
			9/30	20	16	20	0			

*B3 (Dalldorf) = "Nancy" (Melnick).
†A1 (Dalldorf) = Easton 2 and NIH 138 (Melnick and Huebner).
‡A4 (Howitt) = High Point (Melnick).
§+ = positive — but end points not obtained.

another virus recovered occasionally in the endemic area, gave little evidence of antibody elevation in the 6 persons studied. Slight rises in 2 cases were regarded as falling within the error of the test employed.

It will be noted that the correlation of the results of the complement-fixation test with those obtained in the neutralization test was far from complete. Indeed, in many cases there appeared to be little relation between the results of the two tests. This is in accordance with studies reported previously,[20, 21] which demonstrated the superior performance of the neutralization test in reflecting known previous infections with virus. However, it should be pointed out that significant increases in complement-fixation titer occurred in convalescent serums from each of the 7 definite cases of pleurodynia also showing a rise in neutralizing antibodies. The unpredictable eases spread by personal contact. Thus, Sylvest, on the island of Bornholm, and Pickles, in Wensleydale, England, both practitioners in rural areas, were able to establish epidemic pleurodynia as a distinct nosologic entity. Similarly, the disease pattern of the outbreak in northeastern Texas was most apparent in rural areas where the relations between concurrent and previous cases within the household and among neighborhood contacts could be observed. Despite the lack of precise clinical and laboratory data obtainable only in hospital studies, we believed that the stereotyped similar complaints combined with the spatial and temporal relations between cases provided a reliable basis for establishing the usual spectrum of symptoms associated with pleurodynia. Clinical observations under such circumstances made feasible the performance of epidemiologic studies (to be described in subsequent reports)

designed to test the hypothesis derived previously[9] and supported by the data in this manuscript that the B3 immunologic type of Coxsackie virus is one of the etiologic agents responsible for epidemic pleurodynia. The recovery of B3 virus from 16 of 22 patients with pleurodynia during an epidemic supports the hypothesis that this was the etiologic agent responsible for the Texas outbreak. If one eliminated the 5 patients on whom diagnoses other than pleurodynia were entertained, it can be seen that of the remaining 17 persons, 16 were infected with the B3 virus and only 1 with the ubiquitous A1 strain.

Mindful, however, of the fallacies inherent in drawing conclusions from observations of sick persons alone, which have repeatedly associated both Group A and Group B Coxsackie viruses with clinical poliomyelitis, we believe that epidemiologic studies including control groups are necessary to establish the etiologic relations for such newly discovered prevalent viral agents, however clear-cut the uncontrolled data may appear.

In support of this point of view we can cite our experiences and those of others with the A1 virus. It was not surprising to find early in the initial studies that Group A Coxsackie viruses could be isolated from persons with epidemic pleurodynia. As noted above, the first series of stool specimens to be tested from persons with selected illnesses included four specimens that were positive for the A1 virus. This virus, the first to be discovered by Dalldorf,[27] was recovered in Coxsackie, New York, from 2 patients with paralytic poliomyelitis. Melnick et al.[25] later isolated Coxsackie virus from 28 of 42 (66.6 per cent) persons with diagnoses of poliomyelitis in Easton, Pennsylvania, and 24 of 42 (57.1 per cent) harbored the A1 strain. In our studies in Parkwood, Maryland,[28] and Washington, D. C.,[29] we had encountered the agent in the stools of 7 healthy persons living in 3 adjacent households and in several patients with clinical poliomyelitis. In each of the latter cases the virus was demonstrated in specimens taken several days to a week after hospitalization, but not in specimens taken from the same persons at the time that they were first observed. It is not altogether unreasonable to infer a possible etiologic relation between the A1 virus and epidemic pleurodynia, particularly since several patients included in our illness study showed antibody elevations against this virus. However, in the light of the observations presented above and of previous experiences that have clearly shown the prevalence of this and other Group A Coxsackie viruses, it seems to us an unlikely hypothesis.

To our knowledge this paper contains the first reports of the simultaneous occurrence of Group A and Group B Coxsackie viruses in the same persons. Combined infection with poliomyelitis viruses and Group A viruses[24, 25, 30] and with two Group A viruses[13] have previously been described.

Summary

The recovery of Coxsackie virus B3 from the stools of 16 of 22 persons with signs and symptoms of epidemic pleurodynia, together with evidence of antibody responses, provides a sound basis for the hypothesis that this virus represented the etiologic agent responsible for an outbreak of that disease in northeastern Texas. Furthermore, studies by others have previously reported this and other Group B viruses in persons ill with epidemic pleurodynia. However, to develop fully and test such a hypothesis, it is necessary to perform epidemiologic studies that include observations of comparable control groups.

The recovery of Coxsackie virus A1 from 4 patients, 1 of whom probably had herpangina, and 2 of whom also harbored B3 virus, could not be interpreted as having etiologic significance in epidemic pleurodynia. This virus (A1) is known to be so prevalent that its occurrence under these circumstances was not unexpected. The fact that this agent was the first to be encountered in these studies illustrates clearly the fallacy of deducing etiologic importance whenever a prevalent virus is demonstrated in persons selected because they have a prevalent illness.

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ROENTGENOLOGIC AND CLINICAL ASPECTS OF HYPERPHALANGISM (POLYPHALANGISM) AND BRACHYDACTYLISM

Hereditary Abnormal Segmentation of the Hand

MELVIN I. SHOUL, M.D.,* AND MAX RITVO, M.D.†

BOSTON

THE purpose of this communication is to describe a syndrome that involves the hands and feet and is characterized by more than the normal number of phalanges in the affected finger. This feature of the syndrome is called hyperphalangy or polyphalangy and should be distinguished from polydactyly, in which there are more than the usual 5 fingers in the individual hand. No definitive or etiologic name has been applied to the syndrome. Leboucq,[1] of Belgium, is credited with the description of the first case in 1896. Since that time 39 additional cases have been recorded, chiefly in the German and French literature. The rarity of the condition is evident from the writings of Schinz,[2] Barsky,[3] Birch-Jensen,[4] Bunnell[5] and others, who, despite an extensive experience with clinical and roentgenologic lesions of the extremities, do not mention this entity.

HISTORICAL SURVEY

Leboucq[1] recorded the first case of this syndrome in 1896. His description was based on purely anatomic observations since he lacked the advantages of x-ray examination. The patient was a forty-six-year-old woman with bilateral symmetrical deformities of the hands. The index and middle fingers were markedly shortened. Despite the shortening, these 2 digits each contained 4 instead of the normal 3 phalanges. The extra bones, which were between the proximal and middle phalanges, were shorter and wider than the true middle phalanges. The ring fingers were longer than the others. The metacarpals were normal. Leboucq thought that the individual bones of each phalanx developed by a process of budding; hence the number of bones in each finger could be unlimited. His theory was based on dissections of bats and cetaceans. Vidal,[6] in 1910, described a family tree of 5 generations with 10 cases physically and roentgenographically similar to Leboucq's case. The condition acted as a mendelian dominant, although in certain persons the expected deformity did not occur. There were also 20 cases of clinodactyly or bent fifth finger and various other congenital anomalies such as syndactylisms and hypoplasias of many types in this group of cases.

Drinkwater's[7] report (1916) of four generations of a family is the first account of this syndrome in the English language. He found 8 males and 8 females affected in 43 members of the family. He enumerated the essential anatomic characteristics of the syndrome and stressed the fact that these features seemed to be inherited as a unit with little variation from patient to patient. Dell'Oro,[8] in 1935, recorded 1 case. The patient was a boy who had been brought to the emergency ward after an automobile accident. X-ray study of the extremities was made, and after preliminary examination he was thought to have a fracture of the proximal phalanx of the middle finger. This was later proved to be the extra interphalangeal articulation between the supernumerary phalanx and the true proximal phalanx. In 1937 Lossen[9] found 10 cases in the German literature and added 1 of his own. His review of the literature was exhaustive and detailed. One of his patients had bilateral hammer toes involving the second and fourth toes. Congenital anomalies in other parts of the body were not recorded in his cases. Becker,[10] in 1939, described a family with multiple congenital anomalies of the hand among which there were several cases of hyperphalangism. Fifteen cases during 5 generations were described. The pattern was not uniform, and there was such wide variation in the individual cases that they cannot be considered true examples of the syndrome. In 1941, McGavack[11] presented the case

*Chief resident, First Surgical Service, Boston City Hospital.
†Director, Department of Radiology, Boston City Hospital.

of a forty-year-old married woman whose sister and niece showed similar deformities of the hands. The patient was noted to have slight microcephaly, dorsal kyphosis, girdle-type obesity and changes in the skull that McGavack termed "hyperostosis frontalis" but, as is evident from the reproduction of the roentgenograms of the skull, are in reality characteristic of craniostenosis.

Case Reports

Case 1. Mrs. J. S., a 39-year-old housewife, entered the outpatient department of the Boston City Hospital in 1950 because of progressive bilateral deafness. A diagnosis of

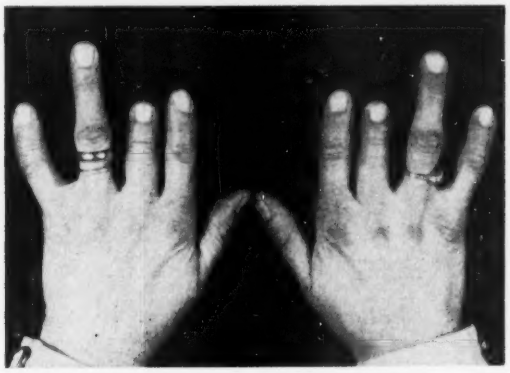

Figure 1. *Dorsal View of the Hands in Case 1, Showing Shortening of the Index, Middle and Fifth Fingers. The little fingers are bent toward the middle of the hand (clinodactyly).*

otosclerosis was made, and the patient was admitted for a fenestration operation. On routine physical examination a bilateral symmetrical deformity of the hands was noted

Figure 2. *Roentgenogram of the Hand (Anteroposterior View) in Case 1, Showing the Characteristic Anomalies of the Syndrome.*

(Fig. 1). The index and middle fingers were abnormally shortened. The ring fingers were longer than the others. The index fingers deviated toward the center of the palm. X-ray studies of the hands were made, and the roentgenograms were interpreted as follows (Fig. 2):

> The middle finger of each hand shows a supernumerary phalanx, the combined length of the 2 proximal phalanges being less than that of the proximal phalanges of the other fingers. The middle phalanges of the index and ring fingers are small and abnormal in shape. The first metacarpal bones are decreased in size. The proximal phalanx of the ring finger of each hand is elongated. The proximal phalanges of the index fingers are long and present a notch-like defect at the proximal ends, with transverse linear bands of increased density at the sites of the previous epiphyseal lines. The ring fingers are longer than normal, whereas the middle fingers are definitely shortened. The little fingers are deviated toward the center of the hand, this change being more marked on the left.

Throughout her lifetime, the patient had shown considerable skill in the use of her hands and was able to do complicated sewing, typing and printing. There had never been any disability resulting from the deformity and she had been able to perform all household tasks without impediment. No other abnormality was discovered on physical examination. She had frequently visited the outpatient department with multiple complaints for which no organic basis could be found and a diagnosis of hypochondriacal anxiety neurosis had been established.

Case 2. R. S., a 17-year-old schoolgirl, was the daughter of the patient described in Case 1. She had been admitted to the Children's Hospital, Boston, Massachusetts, in 1937, at the age of 2 years because of a symmetrical deformity of both hands. This corresponded to the deformity in the mother. The index and middle fingers were markedly shortened and were approximately of the same length as the thumbs. The ring fingers were longer than normal. The terminal phalanges of the small fingers deviated toward the center of the hand. X-ray studies revealed that the index and middle fingers had 4 phalanges. The proximal phalanges of the ring fingers were longer than normal. The metacarpals of the thumbs were

Figure 3. *Appearance of the Hands in Case 2 Fifteen Years after Operation. The index, middle and fifth fingers are shorter than normal. The ring fingers deviate ulnarward, and the fifth fingers are bent toward the center of the hand.*

markedly shortened. The middle phalanges of both hands and toes were brachydactylous. Physical examination disclosed a double-lobed left ear and calcaneovalgus of both feet.

On December 16, 1936, osteotomy of the proximal phalanx of the left ring finger was performed, with removal of a segment of bone. This was designed to shorten the 4th finger to approximately normal length. A similar operation was performed on the right ring finger 1 month later. After the operation the hands presented a more nearly normal ap-

pearance, the index, middle and ring fingers being of approximately equal length. The congenital fissure of the lobe of the left ear was repaired 2 years later.

The patient's mental development was extremely retarded. At 3 years of age, roentgenograms of the skull demonstrated that the posterior fossa was smaller than normal. At the age of 5 years a diagnosis of mental retardation was established. Physical examination at that time disclosed compound myopic astigmatism, hypotonia of the muscles and hyper-reflexia of the joints. Her mental status has never approached normal for her age. The present appearance of her hands, 15 years after operation, is shown in Figure 3. The interphalangeal joints are extraordinarily mobile. The terminal and middle phalanx of the index finger can be dislocated at will from the 2 proximal phalanges of the index finger (Fig. 4). At present, physical examination discloses hypotonia of all muscles, hyper-reflexia and bilateral hammer toe of the 3d toe. X-ray studies (Fig. 5) were carried out, and the roentgenograms were interpreted as follows:

FIGURE 4. *Photograph of the Hands in Case 2, Showing the Thumb and Index Finger Held in Opposition without Force. The terminal phalanx and small middle phalanx are dislocated in relation to the proximal phalanges owing to hypermobility of the joint.*

FIGURE 5. *Anteroposterior Roentgenograms of the Hands in Case 2.*

> The hands show bilateral, symmetrical deformities, with 4 phalanges in the index and ring fingers. In the index finger the supernumerary phalanx appears to comprise a subdivision of the proximal phalanx, whereas in the middle finger there are 2 small phalanges in the region that would normally be occupied by the middle phalanx. The middle phalanges of the little fingers are small and abnormal in shape and structure. The penultimate phalanx of the index finger resembles the middle phalanges of the little fingers of each hand. The 1st metacarpals are shortened. The index and little fingers are deviated toward the center of the hand.

CASE 3. F. M., a 39-year-old unmarried woman was a cousin of the patient in Case 1, and the physical appearance of the hands was identical in both cases. The index, middle and small fingers were shortened and approximately the same length as the thumb. The 4th finger was unusually long. Roentgenograms of the hands (Fig. 6) were reported as follows:

FIGURE 6. *Anteroposterior Roentgenograms of the Hands in Case 3.*

> There is hyperphalangism (polyphalangism) of the index fingers. The middle and proximal phalanges of the middle finger are malformed. The metacarpals, with the exception of the 2d, are short. There is a supernumerary bone between the greater multangulum and the 1st metacarpal. The ring finger is markedly elongated, and the middle finger is brachydactylous. The index fingers and the little fingers deviate toward the middle of the hand.
>
> X-ray studies of the feet showed the middle phalanges of the left 2d and 5th toes to be absent, the middle phalanges of the other toes being short and broad and the proximal phalanges of the left 2d and 5th toes elongated.

The malformation did not interfere with the function of the hands. This patient was also retarded mentally and had never progressed beyond domestic service with light duties. She had always relied upon her employers to make all important decisions, including those relating to her private life. She refused to have a physical examination and would not permit photographs to be made of her extremities.

ETIOLOGY

The etiology of the wide variety of anomalies of the hands that may appear at birth in this and other congenital syndromes is not clearly understood. These anomalies are best grouped into those that are inherited, those due to noxious influences during pregnancy, and those due to atavism or regression to a more primitive form. In 1905 Farabee[12] demonstrated that in a family with brachy-

dactylism certain anomalies are controlled by inheritance. The most striking example of a mendelian dominant pattern is Hegdekatti's[13] report of six generations of an Indian family in which the malformation comprised a reduction of the digits to one in all four extremities. In 1917 Drinkwater[14] recorded a family with symphalangism dating from the time of Henry VI of England. According to legend, a member of the family had first been noted to have the anomaly in 1453. In 1874, when a tomb was opened during the course of construction on church grounds, the finger bones showed anomalies similar to those found in direct descendants living in a nearby town. Examples of congenital malformations originating as mutations and subsequently inherited along mendelian lines have been recorded in the literature with increasing frequency.

The exact cause of the initial mutation has not been established. There have been numerous experimental demonstrations that anomalies can be produced by injury to the germinal cells, and subsequently there may be transmission of the anomalies through succeeding generations. In 1929 Bagg,[15] by means of x-rays in pregnant mice, produced in several generations of offspring multiple foot anomalies that acted in a mendelian-recessive pattern. Pregnant animals have been subjected to copper or riboflavin deficiency,[16] to massive vitamin A dosage[17] and to selenium and lithium poisoning[18] to produce offspring with deformed extremities. Duraiswami[19] injected insulin into the yolk of chick embryos and caused anomalies in the adult.

Stockard[20] experimentally altered normal development of fish by lowering the temperature or reducing the oxygen supply at different times and thereby produced monsters and twins. He concluded that the type of abnormality that resulted depended on the precise stage of development at the time the stimulus was operative rather than the particular noxious stimulus. Similarly, Bagg's[15] experiments with pregnant mice confirmed the hypothesis that the time rather than the agent was the important factor.

Atavism or inheritance of characters from remote ancestors in the phylogenetic line may be important in the etiology of this syndrome. To account for hyperphalangism on such a basis, however, one must revert to the phalangeal formula of the reptile, since no animal higher than the reptile has more than three phalanges in a single finger or toe nor more than two phalanges in the thumb or great toe.

Leboucq[1] assumed that the anomaly was due to a process of budding with an extra phalanx developing from the proximal phalanx. Pol[21] was of the opinion that the supernumerary phalanx developed as an independent growth of the proximal epiphysis of the proximal phalanx, whereas Gräfenberg[22] stated that the extra phalanx developed from an additional proximal epiphysis of the terminal phalanx. In 1950 Steindler[23] noted that double epiphyses may occur in the metacarpals as well as the phalanges. These accessory nuclei usually fuse with the shaft before adult life is attained. Kanavel[24] expressed the opinion that reduction or increase of the number or fusion of the phalanges is due to disorientation of the embryonic epiphyses of the proximal phalanges.

Discussion

The syndrome consists essentially of five anatomic features: hyperphalangism (polyphalangism), with four rather than three phalanges in the middle finger and sometimes the index finger; brachyphalangism or shortening of certain phalanges (the middle phalanx of each finger and toe is markedly shortened, being about a third the normal length); the proximal phalanx of the ring finger is abnormally long; the base of the proximal phalanx of the index finger articulates with the metacarpal head obliquely and deviates ulnarward; and in preadolescent patients there is an extra, roughly triangular bone at the base of the index finger that probably corresponds to the extra phalanx in the middle finger (this supernumerary bone usually fuses with the proximal phalanx during adolescence). The hand is grossly deformed, and the anomaly is obvious on casual examination. The index, middle and little fingers are short and stubby, being equal in length to the thumb whereas the ring finger is unusually long. There is an extra flexion crease in the middle finger. The interphalangeal joints show hypermobility, with a range considerably greater than normal. The 3 patients described above presented the essential anatomic features and constituted true examples of the syndrome.

Although rare, this syndrome is important and merits more widespread recognition than it has received in the past. It comprises a series of anatomic abnormalities inherited along mendelian-dominant lines. A patient with these anomalies should be told of the likelihood of their appearance in his offspring. Before marriage, the possibilities of transmission of the syndrome should be explained, since failure to do so may result in medicolegal complications. Many states require premarital examination of both participants, and it is unethical to withhold information about contagious or inheritable diseases.

It is important to recognize the disease when such a patient's hands have suffered an injury. The supernumerary bones in the index or middle fingers may be confused with old ununited fractures or synostoses. The clinician should be aware that there is a tendency to an increased number of congenital anomalies in other parts of the body, and survey roentgenograms of the skeleton are essential to determine their location and significance. There is no interference with function because of the deformities, and the patients do not appear to be hampered in manual pursuits.

Summary

Three additional cases of a rare congenital syndrome involving chiefly the hands and manifested by hyperphalangy (polyphalangy) and brachyphalangy are reported.

In typical cases the index and middle fingers are short and stubby and are approximately equal in length to the thumbs. The ring finger is unusually long. There are four rather than the usual three phalanges in the index and middle fingers (hyperphalangy or polyphalangy). There is marked shortening of the middle phalanges of the fingers and toes (brachyphalangy.) Congenital anomalies are frequently present in other parts of the body. Two of the patients in this series were mentally deficient, and the third was markedly psychoneurotic.

The condition is of interest in that the group of skeletal abnormalities is inherited as a mendelian-dominant factor through successive generations with little or no variation. The etiology is unknown.

416 Marlborough Street

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PROLONGED CARDIAC PAIN FOLLOWING THE INTRA-ARTERIAL INJECTION OF PRISCOLINE*

Report of a Case

ELLIOT L. SAGALL, M.D.,† AND HOWARD J. LEWENSTEIN, M.D.‡

BOSTON

PRISCOLINE (2-benzyl-4, 5-imidazoline hydrochloride) has been advocated in the treatment of a variety of conditions. Recently, the intra-arterial injection of this drug has been recommended in the therapy of vasospastic and occlusive vascular diseases.[1-9] It has been suggested that by this route of administration a safe, effective, sustained, maximal dose of the drug may be delivered to the site where it is most needed, with a minimal degree of systemic reactions.

Although systemic reactions have been described after the administration of Priscoline, its toxicity has been considered to be low and the side effects minor and transient. A review of the literature has failed to reveal a well documented report of myocardial necrosis caused by the drug. Because of the seriousness of such a reaction, the following case of prolonged cardiac pain with probable myocardial damage after the injection of Priscoline into the femoral artery is reported.

*From the departments of Medicine and Surgery, Beth Israel Hospital, and the departments of Medicine and Surgery, Harvard Medical School and Tufts College Medical School.

†Assistant in medicine, Harvard Medical School; associate in medicine, Beth Israel Hospital; instructor in medicine, Tufts College Medical School.

‡Assistant in surgery, Harvard Medical School; assistant in surgery, Beth Israel Hospital; assistant in surgery, Tufts College Medical School.

Case Report

H. C. (B. I. H. M31577), a 63-year-old Jewish bartender, was admitted to the hospital on June 21, 1952, because of numbness, pain, coldness and cyanosis of the left foot and leg of 5 days' duration. These symptoms, which had appeared suddenly, awakening him from sleep, and persisted until entry, were not relieved by bed rest or the oral administration of Dioxyline Phosphate (Papaveril Phosphate).

There had been no previous leg pain or intermittent claudication. Hypertension had been present for 17 years, and infrequent attacks of squeezing pain in the anterior portion of the chest, relieved by nitroglycerin, for seven years. In 1949 the patient had been admitted to the Massachusetts General Hospital because of an acute posterolateral myocardial infarction and received anticoagulants and digitalis. Two months later he was rehospitalized because of a pul-

monary infarction. At that time there was no evidence of thrombophlebitis, and all pedal pulses were easily palpable. After discharge from the hospital, he improved and was free of cardiac symptoms except for mild, infrequent episodes of angina pectoris. Digitalis was discontinued in 1950. The patient gradually increased his activities and, during the year prior to the present illness, worked 14 to 18 hours daily. The past history was otherwise noncontributory except for a duodenal ulcer demonstrated by x-ray studies 2 years before admission.

Physical examination revealed a plethoric, elderly, apprehensive man. The blood pressure was 170/80. The lungs were clear. The heart was slightly enlarged, the border of cardiac dullness extending to the left. The rhythm was regular. The sounds were of good quality, and there was a soft, Grade 1 apical, systolic murmur. On the left foot just below the ankle there were areas of blotchy cyanosis. The skin of the foot was shiny and atrophic, with loss of subcutaneous fat. The left leg felt cooler than the right, and the toes of the left foot measured 2° lower than those of the right. Both femoral-artery pulsations were easily palpable and equal. The remaining arterial pulsations were absent in the left leg but were present in the right. The left leg showed pallor on elevation and rubor on dependency. Oscillometric studies were consistent with the clinical impression of arterial occlusion in the left leg at about the level of the knee. Physical examination was otherwise noncontributory.

Urinalyses were within normal limits. The hemoglobin (photometric) ranged from 16.6 to 19.8 gm. per 100 cc. The red-cell count was 6,730,000, and the white-cell count 6850 with a normal differential count. The hematocrit ranged from 55 to 59 per cent and a corrected sedimentation rate was 23 mm. per hour (Wintrobe method). The fasting blood sugar was 102 mg., and the nonprotein-nitrogen 37 mg. per 100 cc. An electrocardiogram 2 days after entry was consistent with an old posterior myocardial infarction (Fig. 1). There was normal sinus rhythm at a rate of 90, with occasional ventricular premature beats. Prominent Q waves and inverted T waves were present in Leads 2, 3 and aVF. The ST segments showed slight downward displacement in Leads aVL, V_4, V_5 and V_6. The T waves in the precordial leads were upright.

On the 2d and 3d hospital days, the left lumbar paravertebral sympathetic ganglions were blocked with procaine, without objective change in the peripheral circulation. During this period the patient was also given Priscoline, 25 mg., 4 times a day by mouth, with neither beneficial nor adverse effects.

On the fourth hospital day Priscoline was injected into the left femoral artery in an attempt to improve the collateral circulation of the leg. The artery was easily entered with a 21-gauge needle. On puncture the plunger of the syringe was forced backward by pulsating, bright-red blood; 35 mg. (1.5 cc.) of Priscoline solution was quickly injected. Within 20 seconds, the patient stated that he felt a burning sensation of the left upper thigh, and a diffuse redness appeared over this area. No changes were noted in the contralateral extremity. The sensation of warmth extended to the knee, and there was no evidence of any systemic effect. Five minutes after the intra-arterial injection, however, the patient suddenly became extremely apprehensive and restless, complaining of severe, pressing substernal pain. Examination revealed a heart rate of 130 per minute, with frequent premature beats. The blood pressure was 150/100. A few minutes later, the face became flushed, and the patient complained of a generalized feeling of warmth and burning and dryness of the mouth. The chest pain persisted for 1½ hours and was not relieved by tablets of nitroglycerin, (0.0003 gm.) sublingually but subsided gradually after 100 mg. of meperidine hydrochloride (Demerol) had been administered intramuscularly. The blood pressure remained at 140/90 to 160/110. About 10 minutes after the onset of chest pain, however, the blood pressure on 2 readings fell to 110/60 and then promptly returned to the previous levels. The tachycardia persisted for several hours, but the premature beats gradually diminished in frequency. The patient was extremely apprehensive and had a feeling of impending death, but he did not complain of vertigo or dizziness or become cold, sweaty or clammy.

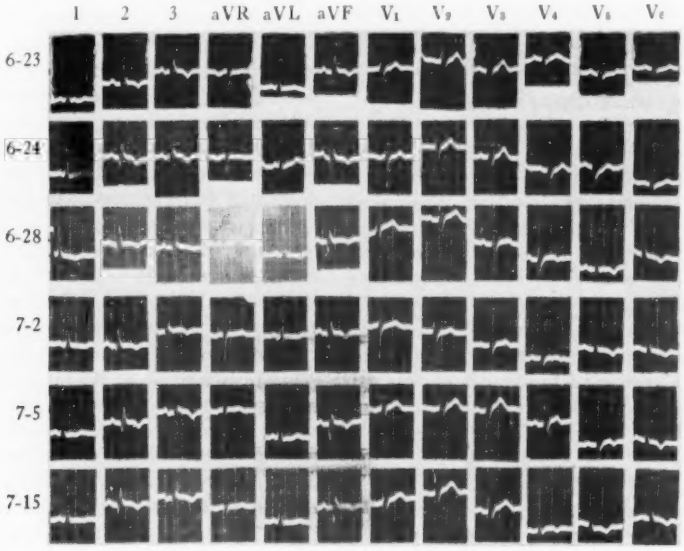

FIGURE 1. *Serial Electrocardiograms before and after Intra-arterial Injection of Priscoline.*

An electrocardiogram taken 4 hours after the episode of chest pain showed only slight changes from the previous tracing, consisting mainly of downward displacement of the ST segments in Leads 1 and aVL. An electrocardiogram 4 days later demonstrated return of the ST-segment displacement and development of inverted T waves in Leads 1, aVL, V_4, V_5 and V_6. In subsequent electrocardiograms the T-wave inversion in Leads 1 and aVL gradually diminished, but inverted T waves in Leads V_4, V_5 and V_6 persisted. The sedimentation rate (corrected) on the 7th hospital day was 15 mm. per hour, but it was 36 mm. per hour on the 12th day and 35 mm. per hour on the 16th day. During the 7 to 10 days subsequent to this attack, the patient suffered mild

short episodes of pain in the anterior portion of the chest that were relieved by nitroglycerin. There were no other cardiac symptoms or signs.

On the 13th hospital day, definite signs of thrombophlebitis in the left leg appeared, consisting of marked calf tenderness, positive Homans sign and pitting edema of the foot. Heparin (75 to 100 mg. every 8 hours) was administered intravenously during the next 4 days and then was omitted because of the appearance of occult blood in the stools. On the 18th hospital day, a bilateral common-femoral-vein ligation and periarterial sympathectomy were performed under local anesthesia. The femoral vein was found adherent to the artery. When the vein was dissected free and opened, blood did not flow from its distal end even after aspiration. No clot was visible or palpable. Pulsations were not palpable or visible in the femoral artery below the inguinal ligament although they were readily palpable above that level. There was no evidence of periarterial hematoma at the site of the intra-arterial injection.

The patient was kept in bed for 3 weeks after the acute myocardial infarction. He was then allowed out of bed and was discharged home for convalescence on the 28th hospital day.

Discussion

In this case the appearance of severe, prolonged chest pain in association with generalized flushing, apprehension and tachycardia approximately five minutes after the intra-arterial injection of Priscoline suggests that these symptoms were precipitated by the administration of the drug. The pulsation of bright-red blood in the syringe after injection and the initial appearance of flushing and warmth only in the injected limb indicate that the injection was truly intra-arterial and not intravenous. The dose of 35 mg. was within the therapeutic range (20 to 50 mg.) employed by most investigators. The absence of side reactions during the previous two-day period of Priscoline therapy by mouth probably indicates that there was no sensitivity to the drug. Clinically the episode was typical of prolonged myocardial ischemia, with probable myocardial damage. The persistence for at least three weeks of inverted T waves, which developed in Leads V_4, V_5, and V_6 within four days of the onset of cardiac pain, and the elevation of the sedimentation rate are consistent with this clinical impression. Whereas the exact pathologic state of the myocardium is unknown, since the patient survived, the phenomena observed during and after the attack make it likely that some myocardial necrosis existed. Although the clinical episode resembled acute myocardial infarction, the absence of characteristic electrocardiographic changes — that is, the development of Q waves — does not permit this diagnosis.

Toxic manifestations resulting from temporary alterations of cardiovascular function have been described after the administration of Priscoline, but a search of the literature has not revealed any detailed account of myocardial necrosis that could definitely be ascribed to the drug. Grimson et al.[10] reported 2 cases in which myocardial infarction developed during oral and intravenous Priscoline therapy. In neither of these patients, however, was there clear-cut evidence of a definite time sequence relating the infarction to the administration of Priscoline; the authors' impression was that myocardial infarction would have developed if the drug had not been used. Lippman[8] stated that with intra-arterial administration of more than 20 mg. of Priscoline in the leg and 12.5 mg. in the arm, unpleasant or dangerous side effects were not uncommon. Included in these reactions was "anginal pain" with abnormal electrocardiographic changes. Prandoni[11] administered Priscoline intra-arterially to 2 patients who had had previous myocardial infarcts, and reported "anginal pain" lasting for thirty minutes in 1 and for three hours in the other after the injections. Recovery in both cases was complete, with no clinical evidence of permanent myocardial damage. Pallor, weakness, sweating, apprehension, palpitation, giddiness, vertigo, rise in blood pressure, hypotension, tachycardia, premature ventricular beats and electrocardiographic changes have been described by various authors after parenteral administration of Priscoline.[4, 5, 8-14] These reactions, however, have been temporary and without serious consequences.

Caution has been advised when Priscoline is administered parenterally to patients with coronary-artery disease chiefly because myocardial ischemia may result from a fall in blood pressure induced by the drug. The possibility that Priscoline will affect the heart adversely in the absence of a hypotensive reaction is suggested by two reports. Flasher et al.[9] recorded electrocardiograms in 13 patients during a five-minute period after the intravenous injection of 50 mg. of Priscoline, and found ST-segment deviations or T-wave alterations in Leads V_5 and V_6 in 5 patients and ventricular arrhythmias in 2 others; the authors concluded that the electrocardiographic changes, which were not related to alterations in pulse rate or to hypotension, presumably represented a direct action of Priscoline on the myocardium. The 2 patients in Prandoni's series[11] in whom anginal pain developed did not show significant hypotension; in 4 other patients, multiple ventricular beats were found after rapid intra-arterial injection of the drug, without the occurrence of hypotension.

In the case reported above, the exact mechanism by which myocardial damage was produced was not established. Clinical observations during the attack revealed only a prolonged tachycardia, with many premature beats, and a slight, only transient, drop in blood pressure. This suggests that the myocardial damage resulted either directly from the effect of the drug or indirectly from a discrepancy between myocardial demand and coronary blood supply created in a patient with pre-existing coronary-artery disease by an increased cardiac output associated with the tachycardia, or the maintenance of blood pressure in the face of peripheral vasodilatation, or emotion precipitated by the symptoms of a systemic reaction.

The very nature of organic vascular disease and the vagaries of its course and complications make it extremely difficult to assess the value of any specific mode of therapy or therapeutic agent. The symptoms of arterial insufficiency often improve spontaneously with the natural development of collateral circulation. For this reason, despite initial encouraging reports, the effectiveness of intra-arterial administration of Priscoline has not yet been definitely established, and this technic of treatment of organic vascular disease must still be regarded as experimental. Although most investigators have stressed the safety of this method of administering Priscoline, systemic reactions are encountered frequently. Indeed, Lippmann[8] observed repeated systemic reactions after intra-arterial injections of less than 10 mg. of the drug in about 15 per cent of his patients. In patients with coronary-artery disease such reactions may lead to serious myocardial damage as a result of ischemia after hypotension or tachycardia, or because of a direct cardiac effect of the drug. It is apparent from this case and from others in the literature that myocardial anoxia has occurred in patients subjected to parenteral administration of Priscoline. In cases of coronary-artery disease, the potential danger of this form of treatment seems to outweigh its uncertain beneficial effects. It is our opinion, therefore, that intra-arterial injection of Priscoline should not be given to patients with known coronary-artery disease. Furthermore, because there is a high incidence of significant coronary atherosclerosis in the older age groups, even in the absence of cardiac symptoms, it seems advisable not to employ this form of therapy in elderly patients.

Thrombotic occlusion or permanent damage to the injected artery has not been reported after this treatment, but "minor" changes such as the development of a perivascular hematoma or a local thrill have been mentioned.[8, 11] In this patient the opportunity of examining the femoral artery under direct observation was afforded two weeks after the intra-arterial injection. At operation, adhesions were found within the femoral sheath, and no pulsation was felt in the femoral artery below the inguinal ligament. At the time of injection the artery had been patent and pulsations easily felt. Although this subsequent femoral-artery thrombosis may have represented proximal extension of the original arterial process, it is extremely probable that the trauma of the intra-arterial injection was responsible for the arterial occlusion.

Summary

A case of prolonged cardiac pain with myocardial damage that clinically resembled acute myocardial infarction after the injection of Priscoline into the femoral artery is reported. Evidence suggesting the development of arterial thrombosis at the injection site is also presented.

Because of the potential danger of the occurrence of a systemic reaction to this drug, in patients with coronary atherosclerosis, it is recommended that the use of intra-arterial Priscoline be discontinued in patients with known coronary-artery disease and in all elderly patients.

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ADAMS–STOKES SYNDROME DUE TO VENTRICULAR FIBRILLATION AND TACHYCARDIA*

MAJOR STEPHEN J. BERTE (MC), U.S.A.,† AND ANNE T. SMITH, M.D.‡

NEW YORK CITY

TRANSIENT ventricular fibrillation is now one of the well established causes of the Adams–Stokes syndrome. This fact has recently been documented by Robertson and Mathews,§ who thoroughly reviewed the literature from 1917 to 1952. They reported a total of 51 cases of Adams–Stokes syndrome associated with ventricular fibrillation or prefibrillary ventricular tachycardia. The following case again emphasizes the need for electrocardiographic verification of the cardiac mechanism during an Adams–Stokes seizure.

CASE REPORT

On September 17, 1952, a 51-year-old housewife, was taken to the hospital from a physician's office immediately after a syncopal attack with a convulsive seizure. On admission, a history of previous seizures of any type was denied. was given daily for 2 days, followed by 0.2 mg. daily for the succeeding 8 days. At the same time, she received 15 drops of "iodine" daily. One day before admission these drugs were discontinued, and quinidine sulfate was given orally in doses of 0.2 gm. every 2 hours for 6 doses. On the day of admission she received 1.2 gm. of quinidine sulfate in 3 equal doses at 2-hour intervals. The last dose of quinidine was taken 1 hour before the seizure.

When first seen at the hospital, the patient had recovered from her seizure. She was slightly apprehensive, well nourished and in no distress. Findings on physical examination were bilateral exophthalmos, a superficial abrasion over the left forehead and well healed thyroidectomy and appendectomy scars. Examination of the heart revealed no enlargement, a regular rate at 80 per minute, no murmurs and a blood pressure of 140/70. The lungs were clear and resonant, and no masses or enlarged viscera were palpable in the abdomen. Neurologic examination was negative. There were no other significant findings.

Examination of the blood showed a red-cell count of 4,630,000, with a hemoglobin of 14.5 gm. per 100 cc., and a

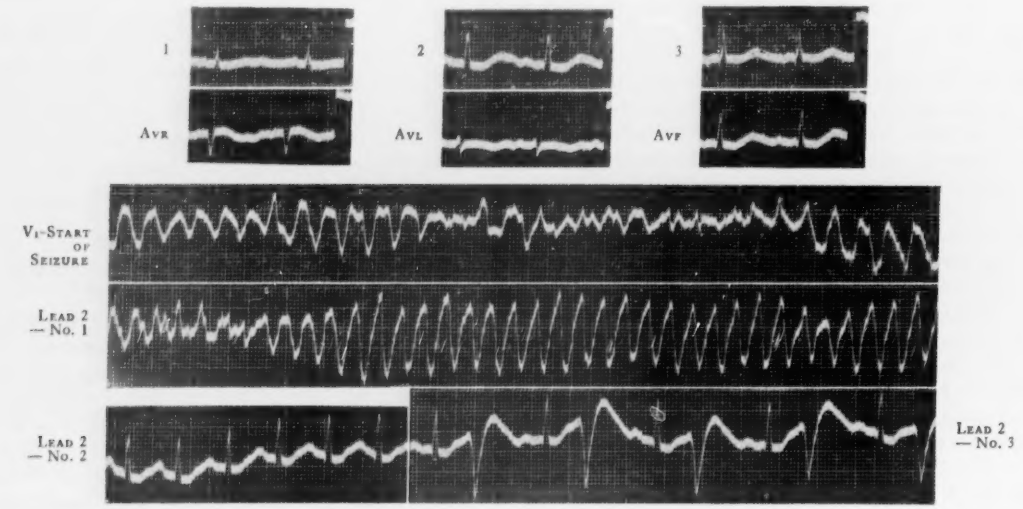


FIGURE 1. *Standard Limb and Unipolar Limb Leads, Showing a Regular Sinus Rhythm, with a Ventricular Rate of 75 Per Minute. A wandering pacemaker is present, the PR interval varying from 0.14 to 0.22 second. No Wenckebach phenomenon is seen. Just as Lead V_1 was about to be taken, a seizure developed, and the tracing taken at that time is shown above. Lead 2 — No. 1 was taken within a few seconds. The tracing was observed throughout the seizure, lasting forty-five to fifty seconds; at no time was there a period of ventricular asystole. Lead 2 — No. 2 was taken immediately after the seizure, and Lead 2 — No. 3, recorded two minutes later, again showed first-degree heart block and bigeminal rhythm.*

Except for a thyroidectomy in 1928 and an appendectomy in 1948, the patient had been well. Since 1950, she had experienced periodic, transient "palpitations of the heart." For these palpitations, she had occasionally been given quinidine by mouth in doses of 0.2 to 0.4 gm. daily. Ten days before admission the patient again consulted her physician because of palpitation. At that time, digitoxin, 0.4 mg.,

*From the Department of Medicine, St. Vincent's Hospital.

†Senior resident in medicine, St. Vincent's Hospital.

‡Resident in medicine, St. Vincent's Hospital.

§Robertson, E. S., and Mathews, E. C. Paroxysmal ventricular fibrillation producing Adams-Stokes syndrome. *Arch. Int. Med.* **90**:320-346, 1952.

white-cell count of 6400, with 66 per cent neutrophils and 34 per cent lymphocytes. The serum sodium was 138 milliequiv., the serum potassium 5.3 milliequiv., and the serum chloride 104 milliequiv. per liter. The blood sugar was 96 mg., the blood urea nitrogen 9 mg., and the total cholesterol 230 mg. per 100 cc.

Approximately 1 hour after admission, it was noted that the heart rhythm, which had previously been regular, was coupled. Bigeminy was recorded on an electrocardiogram. An ectopic ventricular complex followed each normal sinus complex. The auricular rate, measured in Lead V_1, was 90 per minute. Every other sinus beat was absent because it fell during the refractory period of the premature ventricular

beat. First-degree heart block was present, with a PR interval of 0.22 second. The QT interval was prolonged, measuring 0.44 second in Lead I and 0.52 second in Leads V_2 and V_3. The patient's first convulsive seizure in the hospital occurred immediately after this electrocardiogram had been taken. Thereafter, she continued to have syncopal attacks, with generalized convulsions at intervals of approximately 20 minutes. During the attacks she ceased talking, her eyes deviated upward and to the right, her respiration became stridulous and then ceased; her color became cyanotic, and, after 15 seconds, generalized, low-amplitude, clonic convulsions occurred, lasting for 15 seconds. She then remained motionless for 15 to 20 seconds, and as respirations spontaneously returned, her color became normal and she regained consciousness. During one of these attacks, the stethoscope was placed on the chest, and it was noted that bigeminal rhythm ceased, together with all heart sounds. Only a distant, low-pitched, rumbling noise was heard that could not be definitely distinguished from adventitial sounds. At the time respirations resumed, regular heart beats, at 20 beats per minute were heard. This rate gradually increased to a regular rate of 100 per minute, and, within a few minutes, the bigeminal rhythm was resumed.

During the time that a repeat electrocardiogram (Fig. 1) was being taken, the patient experienced a syncopal attack with a seizure. The convulsion occurred while Lead V_1 was being taken. Because of somatic interference, the tracing was immediately shifted to Lead 2. In view of the fact that the seizures were due to ventricular tachycardia and fibrillation, instead of ventricular asystole, no immediate therapy was given.

The interval between attacks increased, and 8 hours after admission, the patient had had no further seizures. She remained asymptomatic for 1 week. An electrocardiogram taken on the 5th hospital day is shown in Figure 2.

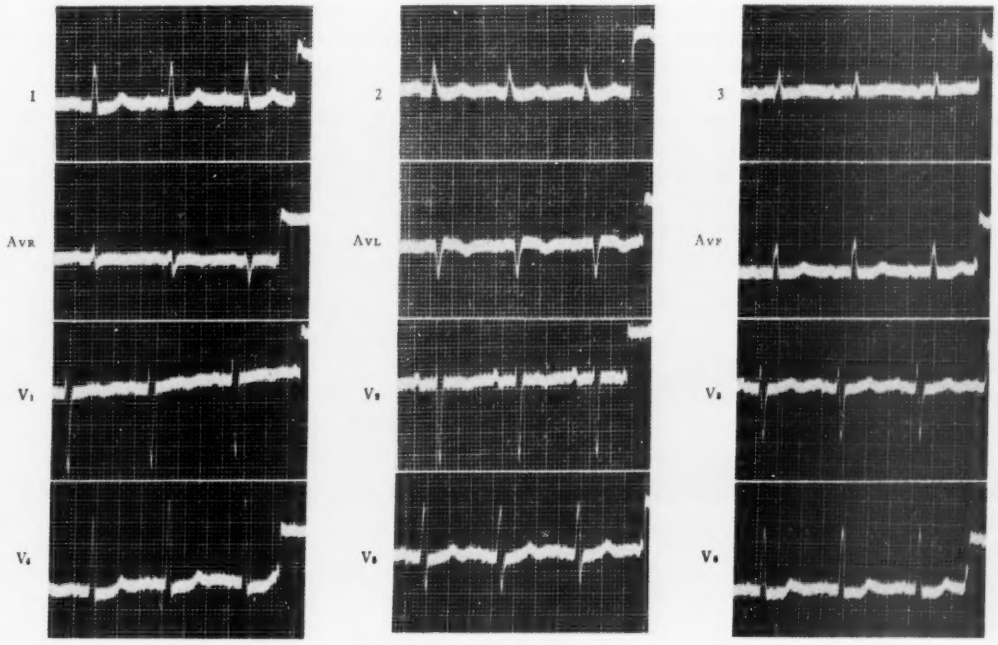


FIGURE 2. *Electrocardiogram Taken Five Days after Admission, Showing Regular Sinus Rhythm, with a Ventricular Rate of 82 per Minute.*

The heart is vertical. The PR interval is 0.20 second, and the QT interval 0.36 second. All findings in this tracing fall within normal limits.

DISCUSSION

It is well recognized that the Adams-Stokes syndrome can be caused either by transient complete heart block with ventricular standstill, or by rapid ventricular tachycardia or ventricular fibrillation. If an electrocardiogram is not taken during an attack, it is frequently assumed that the seizures are a result of ventricular asystole. This assumption is particularly strengthened if evidence of heart block is observed in the electrocardiogram taken between seizures. Frequently, treatment is instituted without a direct effort to obtain an electrocardiographic tracing during an "attack." In these cases the usual medication consists of ephedrine sulfate by mouth or epinephrine hydrochloride subcutaneously. On rare occasions, intracardiac injections of epinephrine have been given. When the Adams-Stokes seizure is due to ventricular fibrillation or rapid, ventricular tachycardia (as in the case reported above) the administration of sympathomimetic drugs tends to perpetuate the arrhythmia. Whenever possible, an electrocardiograph should be available and a tracing obtained during the syncopal period of the Adams-Stokes syndrome. In the case reported

above, failure to give any direct or heroic therapy seems to have been the wisest decision.

In this report, the cause of ventricular fibrillation and tachycardia producing frequent Adams–Stokes seizures can only be presumed. The first-degree heart block and prolonged QT interval could have been the result of quinidine therapy. The QRS interval was within normal limits, but one would expect to see a prolongation of this interval before the development of rapid ventricular tachycardia from toxicity due to quinidine. Nevertheless, since both the PR and QRS intervals returned to normal on a subsequent electrocardiogram (Fig. 2), it may be supposed that quinidine was responsible for the transient heart block, prolonged QT interval and ventricular fibrillation with tachycardia. Also, it is noted that all seizures stopped within eight hours of admission to the hospital and have not recurred. Conversely, this patient, who was fifty-one years of age, may have had arteriosclerotic heart disease with an irritable focus in the myocardium causing attacks of ventricular ectopic rhythms and subsequent seizures. When one reviews the electrocardiograms during this hospital admission, the patient's history of paroxysmal palpitations of the heart of two years' duration suggests that the palpitations were due to paroxysmal ventricular tachycardia. Transient first-degree heart block can occur in arteriosclerotic heart disease, and prolongation of the QT interval is an early sign of quinidine effect that, in itself, does not imply toxicity to quinidine. We believe that quinidine sulfate may have caused the ventricular fibrillations and tachycardia with Adams–Stokes seizures in this case but admit that this is only an opinion and cannot be proved, as pointed out in the foregoing discussion.

Summary and Conclusions

A case of Adams–Stokes syndrome due to ventricular fibrillation and tachycardia is reported.

The electrocardiogram is indispensable in differentiating seizures due to ventricular fibrillation from those due to ventricular asystole. In each condition, this differentiation is significant because of the marked variations in indicated therapy. It is suggested that the electrocardiogram be used in every case of Adams–Stokes syndrome to establish the specific type of arrhythmia causing the seizures.

MEDICAL PROGRESS

PHARMACOLOGIC ASPECTS OF ADRENOCORTICAL STEROIDS AND ACTH IN MAN (Continued)*

George W. Thorn, M.D.,† Dalton Jenkins, M.D.,‡ John C. Laidlaw, M.D.,§ Frederick C. Goetz, M.D.,¶ Joseph F. Dingman, M.D.,|| Walter L. Arons, M.D.,** David H. P. Streeten, M.R.C.P.,** and Brian H. McCracken, M.D.††

BOSTON

Cortisone

Cortisone (Fig. 12) was first isolated from adrenocortical extracts in 1936 almost simultaneously in the laboratories of Kendall,[70] Reichstein[92] and Wintersteiner.[93] Although the drug was nearly devoid of activity, at the dosage levels originally employed, in the maintenance of life in adrenalectomized animals, the demonstration by Mason et al.[70] of the effectiveness of cortisone in the muscle work test of Ingle[94] actually constituted the first evidence of physiologic action in a crystalline steroid of adrenal origin. Subsequently, the synthesis of adrenocortical steroids bearing oxygen atoms in the 11- and 17-carbon positions presented one of the most difficult problems ever undertaken in synthetic organic chemistry. The partial synthesis of cortisone from desoxycholic acid was eventually accomplished in 1946 by Sarett,[95] employing methods extending the procedures developed chiefly by Reichstein[96] and Kendall.[97] The conversion of bile acid to oxygenated corticosteroid entailed four fundamental steps: removal of the side-chain at C-20; the introduction of oxygen at C-11; elaboration of a trihydroxy group at C-17: C-20: C-21, and the subsequent conversion of C-20 to a ketone; and formation of an unsaturated ketone in ring A. Subsequent improvements in the synthetic process made possible the production of cortisone in quantities sufficient

*From the Medical Clinic, Peter Bent Brigham Hospital, and the Department of Medicine, Harvard Medical School.
Supported in part by grants from the National Institutes of Health, United States Public Health Service; the Armour Laboratories; Ciba Pharmaceutical Products; Merck and Company; and the Upjohn Company.
†Hersey Professor of the Theory and Practice of Physic, Harvard Medical School; physician-in-chief, Peter Bent Brigham Hospital.

‡Markle Scholar in Medical Sciences and instructor in medicine, Harvard Medical School; junior associate in medicine, Peter Bent Brigham Hospital.

§Ayerst, McKenna and Harrison Research Fellow and research fellow in medicine, Harvard Medical School; assistant in medicine, Peter Bent Brigham Hospital.

¶Damon Runyon Memorial Fund Research Fellow and research fellow in medicine, Harvard Medical School; assistant in medicine, Peter Bent Brigham Hospital.

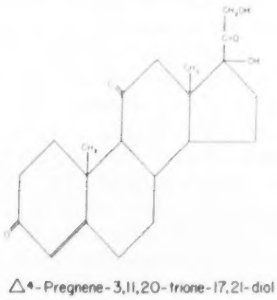
||Dazian Medical Foundation Research Fellow and research fellow in medicine, Harvard Medical School; assistant in medicine, Peter Bent Brigham Hospital.

**Research fellow in medicine, Harvard Medical School; assistant in medicine, Peter Bent Brigham Hospital.

††Formerly, research fellow in medicine, Harvard Medical School, and assistant in medicine, Peter Bent Brigham Hospital.

for clinical trial by 1948. Thus, twenty years after the initial preparation of effective adrenocortical extracts, the isolation, chemical characterization, partial synthesis and finally large-scale production of this highly active steroid hormone were accomplished. Recent advances in this remarkably complex field include the complete synthesis of cortisone[98] and the utilization of micro-organisms for enzymatic oxygenation at C–11.[99] The latter ingenious procedure has been successfully adapted for large-scale production.

The immediate application of cortisone followed two general lines of investigation: an analysis of its important metabolic effects and its efficacy as substitution therapy in patients with chronic adrenocortical insufficiency[100, 101]; and an exploration of its possible usefulness in the treatment of rheumatoid arthritis[102] and other inflammatory diseases.[103] These studies have provided a considerable knowledge of the physiologic effects of cortisone in man, but have as yet given little insight into the precise mechanisms by which these effects are produced. It seems inevitable, however, that an eventual understanding of the divers influences exerted by cortisone on a wide variety of diseases depends upon the successful delineation of the fundamental actions (or action) that the hormone exerts on the mechanisms of cellular metabolism. Although this ideal is admittedly distant, it is quite apparent that the advent of cortisone as a therapeutic agent of striking, even dramatic, consequences has already contributed significantly to the study of metabolic processes on the one hand and of pathologic processes on the other.



Δ⁴-Pregnene-3,11,20-trione-17,21-diol

FIGURE 12. *Chemical Structure of Cortisone (11-Dehydro-17-Hydroxycorticosterone).*

PHYSIOLOGIC ACTIONS

The physiologic actions of cortisone may be discussed conveniently under four headings: the influence of this hormone on intermediary metabolism; its effects on specific tissues; its influence on growth; and its effects on mechanisms of defense.

Intermediary Metabolism

Organic metabolism.

Carbohydrate metabolism: The classic experiments of Long, Katzin and Fry[104] showed that adrenal insufficiency in animals is characterized by low blood glucose levels during fasting, depletion of liver but not muscle glycogen, decreased excretion of urinary nitrogen, high standard respiratory quotient and increased sensitivity to insulin. Similar findings in patients with Addison's disease were reported by Thorn et al.[73] In both instances the metabolic disturbances could be reversed by the administration of cortisone.

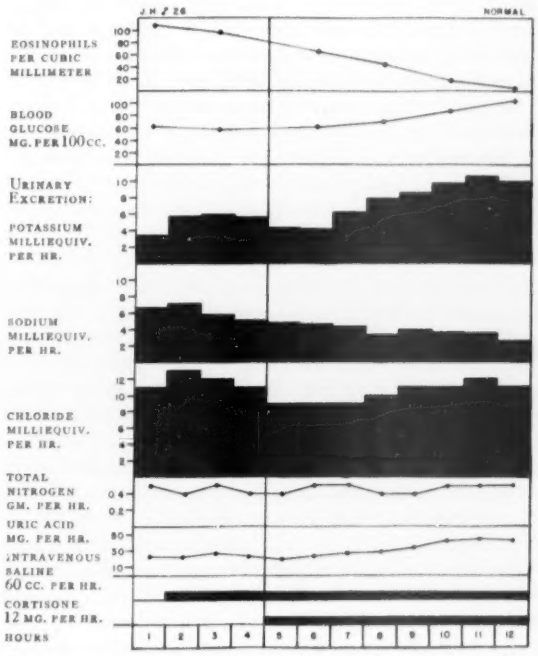

J. H. Z. 26
NORMAL
EOSINOPHILS PER CUBIC MILLIMETER
BLOOD GLUCOSE MG. PER 100 CC.
URINARY EXCRETION:
POTASSIUM MILLIEQUIV. PER HR.
SODIUM MILLIEQUIV. PER HR.
CHLORIDE MILLIEQUIV. PER HR.
TOTAL NITROGEN GM. PER HR.
URIC ACID MG. PER HR.
INTRAVENOUS SALINE 60 CC. PER HR.
CORTISONE 12 MG. PER HR.
HOURS
1 2 3 4 5 6 7 8 9 10 11 12

FIGURE 13. *Result of Intravenous Cortisone Infusion in a Normal Subject.*

The patient was fasting throughout the experiment. All urinary analyses were performed on one-hour collections.

There is little doubt that the influence of cortisone on carbohydrate metabolism may be explained in part by its ability to stimulate gluconeogenesis from protein. This is indicated by the coexistence of increased excretion of urinary nitrogen and increased glycogen stores in animals and human beings after cortisone administration. Further support for the view that this hormone influences gluconeogenesis has recently been provided by Welt et al.,[105] who showed that cortisone-fed rats given a

constant infusion of C-14-labeled glucose increased liver glycogen from some source other than body glucose. That cortisone may accelerate gluconeogenesis from fat has been indicated by Kinsell et al.,[106] who demonstrated that in diabetic patients maintained on carbohydrate-free diets the hormone may produce a degree of glycosuria in excess of that readily explicable on the basis of gluconeogenesis from protein alone. It is of interest in this connection to note the wide discrepancy between nitrogen excretion and blood sugar level resulting from the intravenous infusion of cortisone over an eight-hour period in a normal fasting subject (Fig. 13).

In addition to its effect on the stimulation of gluconeogenesis, it has been felt[107] that cortisone must inhibit some phase of carbohydrate utilization (storage as glycogen, oxidation to carbon dioxide and water or conversion to fat and protein). This view has been supported by the following evidence: the observation that cortisone will cause a fall in the respiratory quotient in animals[104] and human beings,[73] the finding that cortisone suppresses the tolerance of the eviscerated rat for intravenously administered glucose[108] and the observation that there is a decreased conversion of carbohydrate to fat in the cortisone-fed, intact animal.[109] It is not clear whether the inhibitory effect of cortisone on carbohydrate utilization is exerted at the initial reaction involved in glucose uptake by tissues — namely, the hexokinase reaction — or at some other point in the metabolic pathway of glucose. That the hormone may inhibit the conversion of carbohydrate to fat at a point other than the hexokinase reaction has been indicated by the observation of Brady et al.[110] that the incorporation of C-14-labeled acetate by rat-liver slices into long-chain fatty acids is inhibited by the previous injection of cortisone.

In a discussion of the influence of cortisone on carbohydrate metabolism, the relation of this hormone to diabetes mellitus is of particular interest. Long and Lukens[111] were the first to show conclusively that adrenalectomy decreases the severity of pancreatic diabetes. Glycosuria is diminished, and there is a marked increase in insulin sensitivity. That this is also true in man has been demonstrated in patients with coexisting Addison's disease and diabetes mellitus.[112, 113] The onset of adrenal insufficiency in diabetic patients is marked by a decreasing insulin requirement and by an increased tendency to hypoglycemic reactions of unusual severity in addition to the usual symptoms of Addison's disease. On the other hand, Long et al.,[111] in 1940, observed that the glycosuria of the partially depancreatized rat could be intensified by cortisone. Shortly thereafter Ingle[114] reported the production of glycosuria in force-fed normal animals by the administration of cortisone. Of particular interest to the clinician are the more recent observations made in both normal subjects and diabetic patients during the administration of ACTH or cortisone. Conn and his collaborators[115] have shown that the administration of ACTH in doses of 75 to 150 mg. daily for five to ten days may produce, in normal subjects, fasting hyperglycemia, glycosuria and diminished tolerance to carbohydrate. The clinical diabetes thus produced was further characterized by a renal component of glycosuria, by a marked degree of insensitivity to insulin and by its complete reversibility upon discontinuance of hormone administration. Although Conn's observations have been confirmed by a number of investigators, the general opinion has been that such marked diabetic responses are the exception rather than the rule in normal subjects or patients without evidence of pre-existing diabetes. For example, in a series of 27 patients with rheumatoid arthritis, Sprague et al.[116] found that the prolonged administration of cortisone in doses of 100 to 200 mg. daily caused slight and inconsistent increases in fasting blood glucose and decreased glucose tolerance of a mild degree in only 4 patients. Similar findings have been reported by Wilson and his associates,[117] who concluded that the functional reserve of the pancreatic islets is usually sufficient in normal subjects to compensate for the diabetogenic action of cortisone.

Protein metabolism: Fasted adrenalectomized animals and patients with Addison's disease[73] exhibit a decreased urinary nitrogen excretion that can be reversed by the administration of cortisone. In addition, it has been repeatedly shown that large doses of cortisone in the intact organism will lead to a negative nitrogen balance. It should be emphasized, however, that this response may be diminished by the feeding of high-carbohydrate or high-protein diets and by the administration of supplementary potassium.[118] The precise mechanisms by which cortisone increases urinary nitrogen excretion are not clearly understood. Hoberman,[119] in studies of the effect of cortisone administration on the fate of injected isotopic glycine in adrenalectomized animals, reported both a stimulation of protein catabolism and an inhibition of anabolism. The latter observation supports the hypothesis first proposed by Albright.[120] Hoberman was unable to detect any abnormality in amino acid catabolism in adrenalectomized rats. The finding of a lessened accumulation of amino acids in the plasma of hepatectomized-adrenalectomized rats[121] likewise emphasizes the antianabolic action of the 11,17-oxysteroids such as cortisone. The observation[122] that cortisone will restore to normal the diminished activity of liver amino acid oxidase in adrenalectomized animals indicates, however, that this hormone may act in part at the amino acid level of nitrogen metabolism.

After intense stimulation of the adrenal cortex in man, there is a greatly increased urinary excretion of histidine, glutamine, alanine, threonine, glycine, serine, lysine and small increases in glutamic

and aspartic acids, glycine, cystine and methionine.[123] The associated rise in serum amino acid nitrogen indicates that the hormone action is not limited to its effect on renal threshold.[124] The increase in urinary cystine and methionine accounts for only 50 per cent of the increase in urinary organic sulfur.[125] After ACTH administration in man, there is also a rise in the urinary total sulfate which may be due in part to an increased urinary output of sulfuric acid conjugates of adrenal steroids.

Little is known of the influence of cortisone on purine and pyrimidine metabolism. It has been shown, however, that the administration of this hormone to normal human beings[116] and to patients with Addison's disease[7] leads to an increased urinary excretion of uric acid (Fig. 13). In some subjects little change in serum uric acid level was noted, suggesting an increase in urate formation or mobilization. Studies with isotopic uric acid in a patient with gout[126] indicated that the effect of 11,17-oxysteroids such as cortisone on uric acid metabolism is predominantly one of increased renal clearance rather than increased production.

Lipid metabolism: Studies on the influence of cortisone on lipid metabolism have been meager, and their interpretation difficult. Levin and Farber[127] showed that the livers of fasting adrenalectomized rats contained considerably smaller quantities of neutral fat than those of intact animals; pretreatment with cortisone prevented this disturbance. The administration of large doses of cortisone was found to cause intense lipemia and fatty livers in intact rabbits[128] and slight increases in neutral fat in the livers of normal rats.[127] These observations have been interpreted in the past as indicating a low rate of fat mobilization and catabolism in the adrenalectomized animal that can be reversed by cortisone. Stoerk and Porter,[129] however, found that partially starved adrenalectomized rats showed less neutral fat in both liver and *carcass* than intact animals on isocaloric diets. This finding of a low body fat in adrenalectomized animals must indicate either a diminished liponeogenesis or an increased catabolism of fat. Welt and Wilhelmi,[109] from a study of the uptake of deuterium into liver and carcass fat by adrenalectomized rats on high-carbohydrate fat-free diets, concluded that adrenalectomy was followed by an increased rate of lipogenesis from carbohydrate. Thus, it seems that there is increased fat catabolism after adrenalectomy. That the absence of ketosis in the fasting adrenalectomized animal does not invalidate this view may be inferred from the finding of Villee and Hastings[130] that acetate, the chief immediate precursor of ketone bodies, is oxidized to carbon dioxide at a normal rate in the diaphragm of adrenalectomized rats. The observations of Thorn et al.[101] that a rise in blood ketones and a fall in respiratory quotient follows cortisone administration to patients with Addison's disease do not necessarily indicate that this hormone produces an increased oxidation of fat. Similar results might be obtained if there were an increased conversion of fat to carbohydrate or a decreased lipogenesis from carbohydrate. Evidence for such an effect has been provided by Brady et al.,[110] who found that cortisone inhibited the incorporation of C-14 acetate into the fatty acids of rat-liver slices.

Little is known of the influence of cortisone on phospholipid and cholesterol metabolism. Adlersberg et al.,[131] studying the serum lipids in a variety of conditions, observed a gradual increase of total and esterified cholesterol as well as of phospholipid but a sharp decrease of serum neutral fat.

Mucopolysaccharides: The dramatic effect of cortisone in inflammatory processes and on diseases characterized by disturbances in connective tissue is well known. Yet the mode of action in these conditions awaits discovery. Fundamental studies of the influence of this hormone on the metabolism of the constituents of connective tissue, most particularly of the mucopolysaccharides, are fragmentary, and little in the way of a coherent pattern of action has emerged. Cortisone has been observed to restore to normal the high serum level of hexosamine in patients with disseminated lupus erythematosus[132]; the high blood levels of glucosamine polysaccharides, nonglucosamine polysaccharides and albumin polysaccharides in patients with rheumatic fever likewise returned to normal.[133] The changes observed were associated with clinical remission in both studies. Layton[134] has reported that cortisone inhibits the synthesis of chondroitin sulfate, a constituent of the connective-tissue ground substance, by embryonic and healing wound tissue maintained in vitro. The degree of polymerization of the hyaluronic acid of the joint fluid of patients with rheumatoid arthritis is said to be increased after the intra-articular injection of cortisone.[135] An inhibitory effect of cortisone on the activity of hyaluronidase in vivo both in animals and in man has been demonstrated.[136]

Enzymes: Numerous studies on the influence of cortisone on enzyme systems have been reported.[137, 138] The major systems on which an action of this hormone has been clearly demonstrated may be summarized as follows. Cohen[139] reported that cortisone administration in mice and human beings results in an increase in serum glucuronidase activity. Kochakian[140] found that the liver and kidney arginase activity of mice is elevated after the injection of cortisone. Umbreit[141] noted that the low activities of liver amino acid oxidase and kidney proline oxidase of adrenalectomized rats could be restored to normal by the administration of the hormone; this observation is of some interest in view of the known influence of cortisone on collagen and the fact that of all the proteins of the body collagen is characterized by a high proline content.

The inhibitory effect of cortisone on hyaluronidase activity in vivo has already been described. The increased secretion of pepsinogen that follows cortisone administration in man is discussed below.

It is apparent that none of the known effects of cortisone on enzyme systems give a clear picture of the mechanisms involved in the over-all physiologic actions of the hormone. Umbreit[142] points out that in the majority of studies the rates of the various enzymatic reactions tend to be diminished or unchanged after adrenalectomy and to be increased after prior treatment with cortisone. It should be particularly emphasized that no effect of cortisone on enzyme systems has been clearly demonstrated in the absence of the intact cell. This fact raises the possibility that the hormone acts by controlling the access of substrate or co-factors to the enzyme within the cell rather than by a direct action on the enzyme itself.

Inorganic metabolism. The effects of cortisone on electrolyte excretion in man conform, in general, to the metabolic pattern previously described for desoxycorticosterone and other less highly oxygenated adrenocortical steroids: sodium and chloride retention, and enhanced potassium excretion.[7] However, the ultimate effects are considerably more variable and appear to be largely determined by hormone dosage, route and duration of administration and, in all likelihood, by the fundamental state of the adrenal glands in normal persons and the influence of simultaneous desoxycorticosterone therapy in patients with adrenal insufficiency. Early studies in normal and adrenalectomized animals, utilizing small quantities of cortisone acetate for brief periods, conclusively demonstrated that the electrolyte-regulating capacity of this hormone was significantly less intense than that of desoxycorticosterone acetate.[143, 144] Indeed, the net result of cortisone administration was, in most cases, a loss of sodium and chloride. It was therefore concluded that one physiologic consequence of 17-hydroxylation of the corticosteroid structure was a marked decrease in the capacity of adrenal steroids to influence the renal handling of electrolytes. Although subsequent studies in animals[145] and man[116] showed that more prolonged administration of larger doses of cortisone acetate ordinarily result in sodium retention and potassium elimination, the simultaneous administration of desoxycorticosterone acetate and cortisone acetate to patients with Addison's disease has, on occasion, produced less retention of sodium and chloride than the same quantity of desoxycorticosterone acetate alone.[101] In view of the known pharmacologic opposition of these two steroids in their effects on other functions such as electroshock threshold,[146] it is of interest to consider the possibility of steroidal competition at certain loci under proper conditions of dosage and functional organization.

Adrenal insufficiency: The effects produced on electrolyte excretion by the administration of cortisone acetate to patients with Addison's disease are variable and unpredictable, necessitating careful evaluation in individual cases. A relatively small number of patients can be successfully maintained in electrolyte balance on average substitution doses of cortisone acetate (12.5 to 25 mg. a day) and supplementary salt. Similarly, patients with essential hypertension can often be adequately controlled after complete bilateral adrenalectomy by the administration of somewhat larger doses of cortisone acetate (37.5 to 50 mg. a day) and additional salt.[36] However, the majority of patients with Addison's disease and a significant number of hypertensive subjects who have undergone total adrenalectomy require the addition of desoxycorticosterone acetate for the maintenance of adequate electrolyte regulation.[47, 113, 147] Comparative studies based on sodium and chloride retention in patients with Addison's disease have indicated that cortisone acetate has approximately one-thirtieth to one-fiftieth the potency of desoxycorticosterone acetate.[48] Cortisone is somewhat more effective in the control of electrolyte excretion after intramuscular injection than after oral administration, reflecting, apparently, the importance of constant hormonal effect on the renal tubular mechanisms involved.

The effects of maintenance doses of cortisone on potassium excretion in patients with adrenal insufficiency are highly variable. Although an initial slight increase in urinary potassium output may occur, restoration of balance or even a rebound potassium retention rapidly ensues; sometimes, a definite decrease in potassium excretion is encountered. In such cases, it appears that the effects of cortisone on carbohydrate metabolism are predominant over renal changes in electrolyte output and that the positive potassium balance is due to increased storage of liver glycogen. This interpretation is strengthened by the observation that inorganic phosphorus output also frequently declines in association with potassium retention.[7]

Normal subjects and patients with intact adrenal glands: The administration of large doses of cortisone to both normal subjects and patients with intact adrenal glands is ordinarily followed by definite sodium and chloride retention and an increased excretion of potassium.[116, 148] With continued administration of the hormone sodium and chloride retention ordinarily decreases; in fact, a negative balance may occur, as previously described for prolonged courses of desoxycorticosterone acetate. An increase in both urinary and fecal excretion of calcium and phosphorus is usually produced by intensive cortisone administration.[149] Initially, phosphorus output ordinarily exceeds the theoretical excretion of calcium and nitrogen, calculated on the basis of theoretical ratios of calcium to

phosphorus and nitrogen to phosphorus in bone and protoplasm respectively. This phenomenon is in all likelihood due to a significant increase in the renal clearance of phosphorus. Subsequently, however, total phosphorus excretion is often less than that anticipated on the basis of theoretical calculations. It appears probable that the latter effect is the result of a movement of phosphate intracellularly in association with an increase in liver glycogen deposition.[150] On the basis of actual tissue analyses as well as the calculation of internal balances,[149] it is evident that a significant degree of intracellular potassium and phosphorus depletion may be produced. Simultaneously, an intracellular migration of sodium may occur but apparently only in the presence of cellular potassium loss without equivalent phosphorus loss — that is, relative cation depletion.[149] An initial retention of sodium in excess of chloride, without a significant change in serum concentration, is additional evidence of the movement of sodium into cells.

It is apparent, on the basis of the over-all losses of nitrogen, potassium and phosphorus, that intracellular protoplasm undergoes depletion as a result of intensive cortisone action. This effect alone, however, is incapable of accounting for the total pattern of metabolic changes produced. For example, the loss of potassium precedes that of nitrogen and is in excess of the theoretical protoplasmic nitrogen-potassium ratio. This is well illustrated in Figure 13, which shows the initial metabolic responses of a normal fasting subject to intravenously infused cortisone. The discrepancy between the theoretical nitrogen and potassium contents of protoplasm and the observed excretory pattern is obvious. It is of interest to note the rapidity with which maximal changes in electrolyte excretion are produced by the continuous intravenous administration of cortisone. In fact, the effects obtained are only slightly less intense than those resulting from the intravenous infusion of an equal quantity of desoxycorticosterone. This is in direct contrast to the relative potencies of these steroids given by intramuscular injection.[7]

Prolonged administration of cortisone in large doses intensifies the effects described above, resulting in hypochloremia, hypokaliemia and metabolic alkalosis. The changes are similar to those originally described by Kepler[151] in patients with Cushing's syndrome. Simultaneously, the electrolyte content of muscle also resembles that encountered in hyperadrenocorticism: decreased intracellular potassium and phosphorus, with or without increased sodium.[152] The administration of testosterone, either to patients with Cushing's syndrome or to patients receiving large quantities of cortisone, results in a diminution of potassium, phosphate and calcium loss.[153] Evidence has been presented that the beneficial action of testosterone is the result of a direct anabolic influence on protoplasm rather than a block in the metabolic action of cortisone on end organs.[60]

Additional effects on inorganic metabolism resulting from adrenocortical stimulation or the administration of cortisone include a moderate decrease in urinary excretion of magnesium[60] and the production of an acute hypoferremia in dogs[154]; the latter effect has not been observed in human subjects.

Water metabolism. The first physiologic function of adrenocortical hormones to receive emphasis was the regulation of electrolyte and water metabolism.[155] Although it was early recognized that a redistribution of fluid occurred in adrenalectomized animals, resulting in a shift of water from the extracellular to the intracellular space,[156] most authorities attributed this change to uncontrolled salt loss.[157] However, numerous studies concerning the relation of adrenocortical hormones to water metabolism have made it abundantly clear that changes in water distribution cannot be explained solely by an alteration in electrolyte excretion.[158] It is also quite apparent that changes in water excretion after cortisone administration cannot be considered merely a passive response to changing electrolyte levels. For example, cortisone may result in a retention of sodium and water with a consequent expansion of extracellular fluid volume sufficiently great to result in edema. On the other hand, a marked dissociation between the urinary excretion of electrolytes and water sometimes occurs during cortisone administration. Furthermore, since the administration of cortisone in certain circumstances may result in a pronounced water diuresis, it is evident that adrenocortical hormones may exert either a diuretic or an antidiuretic action, depending on the existing physiologic state.

Adrenocortical insufficiency: Striking abnormalities in body-water distribution are apparent in patients with adrenocortical insufficiency, consisting of an expansion of intracellular volume at the expense of extracellular volume. It has never been definitely settled whether this redistribution is the result of a change in external sodium balance, with a consequent osmotic intracellular shift of water, or of an internal movement of salt as well as water from the extracellular fluid space into body cells on the basis of a direct effect at the cellular level. Swingle[159] concluded that an endogenous shift of salt and water from the extracellular compartment into cells in excess of that attributable to hypotonicity secondary to renal salt loss occurred in adrenalectomized dogs. Harrison and Darrow[157] also demonstrated an intracellular movement of water during the development of adrenocortical insufficiency, but attributed it entirely to urinary sodium loss. Recent experiments by Gaudino and Levitt[25] appear to confirm the existence of a combined salt and water shift during adrenal insufficiency.

Since the passage of water into red blood cells would result in a dilution of erythrocyte hemoglobin, and therefore a fall in the mean corpuscular hemoglobin concentration (MCHC),[160] changes in this index have been used in this laboratory to study alterations in the distribution of water in patients with Addison's disease during overhydration.[161] During overt adrenal insufficiency an increase in erythrocyte hydration was apparent, as evidenced by a fall in MCHC. The intravenous administration of cortisone induced a prompt decrease in erythrocyte volume and a rapid excretion of excess body water. These results are in accord with those

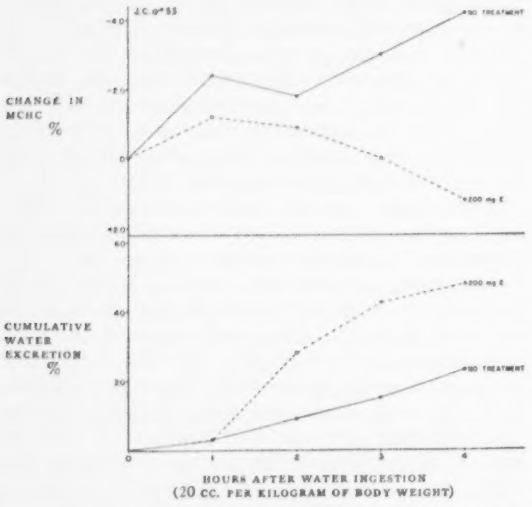


FIGURE 14. *Effect of Cortisone on the Water Test and MCHC in Addison's Disease.*

Cumulative water excretion is expressed as percentage of water ingested. A rise in MCHC reflects a decrease in erythrocyte size.

of Harrop,[156] who showed that adrenocortical extract caused a removal of excess intracellular water, a decrease in mean corpuscular volume and a restoration of normal fluid equilibrium in the adrenalectomized dog.

Rowntree and Snell[162] originally noted, during the course of dilution tests, a decided lag in the onset and extent of water diuresis. The inability to excrete a water load promptly was subsequently made the basis of a useful screening test for adrenal insufficiency.[163] This defect has been the object of numerous studies and has been variously ascribed to: delayed absorption of water from the gastrointestinal tract; a decreased glomerular filtration rate and renal plasma flow; abnormally high levels of antidiuretic substances, on the basis of serum[164] and urine[165] assays; either an increased sensitivity to[164] or decreased capacity to inactivate[166] circulating antidiuretic substances; and abnormality of the renal tubules, resulting in excessive water reabsorption.[158]

Delayed absorption has been ruled out by a lack of diuresis after intravenous injection of fluid[167] and by a normal plasma dilution after water ingestion by patients with Addison's disease.[165] Since the administration of desoxycorticosterone acetate to patients with adrenal insufficiency has been shown to restore glomerular filtration rate to normal without materially improving the rate of water diuresis, a reduced filtration rate can hardly be implicated. Evidence that casts doubt on the importance of circulating antidiuretic substances has been accumulated. Hypophysectomized animals[168] and patients with loss of both anterior and posterior pituitary function[169] evidence a defective diuresis although posterior pituitary hormones are presumably absent. Recently, patients with Addison's disease were shown to have a normal sensitivity to administered Pitressin that was not altered by cortisone administration.[170] Some patients with Addison's disease demonstrate a normal fall in urinary specific gravity after water loading, apparently indicating that persistent tubular reabsorption of water is not wholly responsible for the faulty diuresis observed.[161] In addition, Reforzo-Membrives and Repetto[171] found a normal inhibition of tubular reabsorption of water in patients with Addison's disease in response to water loading.

The finding of an excessive and prolonged trapping of administered water in the erythrocytes of patients with Addison's disease accompanying a failure of diuresis indicates that a defective distribution of a water load may preclude adequate renal excretion.[161] Striking improvement in water excretion occurs in these patients during cortisone therapy,[47] either with no significant change in the depressed glomerular filtration rate[170] or without a direct correlation between improvement in filtration rate and water diuresis.[172] Figure 14 illustrates the effect of cortisone on erythrocyte swelling and water diuresis observed in a patient with untreated Addison's disease. The administration of a water load in this patient produced a marked increase in erythrocyte volume, evidenced by a fall in the MCHC, and a defective water diuresis. A subsequent water test after the administration of cortisone a few hours before the water load brought about a marked improvement in erythrocyte response and a significant increase in the degree of diuresis. These findings suggest that a normal diuresis is facilitated by an improvement in water distribution as a result of cortisone therapy.

Normal subjects and patients with intact adrenal glands: The administration of cortisone to normal subjects induces an increase in extracellular fluid volume,[173] and a decrease in intracellular water content without a marked change in total tissue water.[149] Salt and water retention usually occurs early in the course of treatment and reverts to a normal balance in eight to ten days.[116] The maximal change in body-fluid content and distribution

ordinarily coincides with a maximal increase in glomerular filtration rate and filtration fraction.[173] Cortisone therapy augments the rate of urine flow during constant water loads in subjects with normal adrenal glands, without altering the sensitivity to exogenous Pitressin.[174] It suppresses the normal diurnal rhythm of water and electrolyte excretion in normal subjects.[175]

Further studies on the relation of adrenal oxygenated corticosteroids to the degree of erythrocyte hydration in response to water loading demonstrated that excessive amounts of cortisone-like steroids may induce a paradoxical shrinkage of the erythrocytes despite a normal fall in serum tonicity.

Effects on Specific Tissues

The characteristic changes in specific tissues of the body resulting from the administration of cortisone are obviously consequent to the widespread metabolic alterations just described. It is to be emphasized, therefore, that the use of the hormone in clinical therapy at high dosage levels

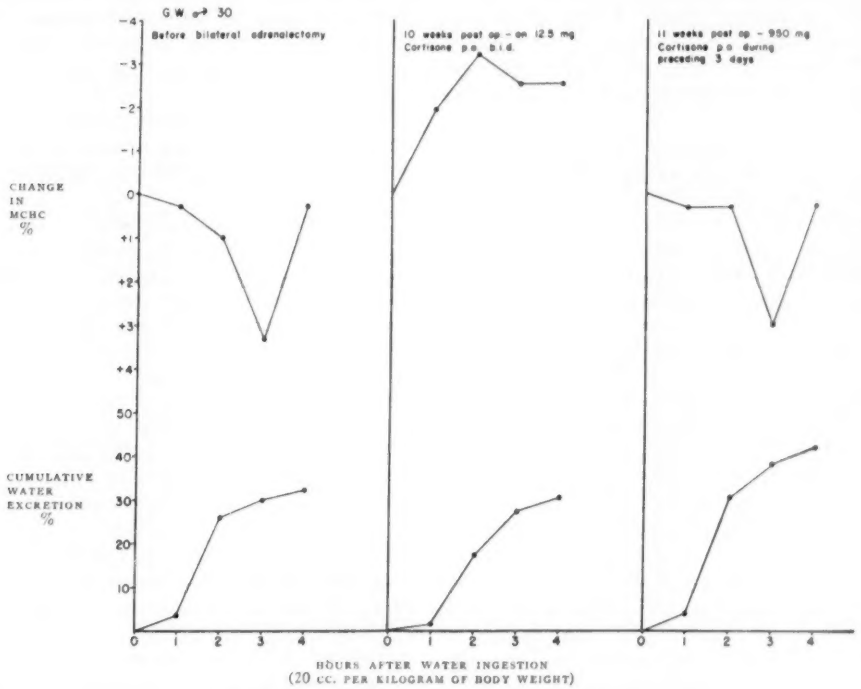

G.W. ♂ 30
Before bilateral adrenalectomy
10 weeks post op - on 12.5 mg Cortisone p.o. b.i.d.
11 weeks post op - 950 mg Cortisone p.o. during preceding 3 days
CHANGE IN MCHC %
CUMULATIVE WATER EXCRETION %
HOURS AFTER WATER INGESTION
(20 CC. PER KILOGRAM OF BODY WEIGHT)

FIGURE 15. *Water Tests in Cushing's Syndrome.*
Cumulative water excretion is expressed as percentage of water ingested. A rise in MCHC reflects a decrease in erythrocyte size.

an actual contraction of erythrocytes during a water test performed on a patient with Cushing's syndrome (Fig. 15).[161] After bilateral total adrenalectomy and the onset of clinical remission from this disease, there was a change in the erythrocyte pattern to one much like that seen in Addison's disease. The administration of large doses of cortisone for a three-day period restored the corpuscular pattern to that seen preoperatively, again with contraction of the erythrocytes in response to water. These findings, in the absence of any significant alteration in the magnitude of water retention or in the degree of hemodilution, suggest that cortisone has an action on the transfer of water into the erythrocytes that is independent of its diuretic effect and entails alterations in the metabolism and potentially in the structure of all tissues. An evaluation of therapy undertaken for the purpose of producing a specific action in a specific tissue or organ system must take into account the over-all effects of the hormone. In short, cortisone affects such a wide variety of metabolic processes and cellular structures that one must interpret any single hormonal action in terms of the aggregate effects on the entire organism.

Effects on kidney.

Adrenal insufficiency: It has long been recognized that defective renal function constitutes one of the major physiologic disorders of chronic adrenal insufficiency. In fact, the degree of azotemia result-

ing from dehydration, hemoconcentration, reduced plasma volume and diminished renal blood flow has often been used as an index of the severity of adrenal insufficiency in adrenalectomized animals. Studies of renal function in patients with Addison's disease have demonstrated a diminished glomerular filtration rate, and a less marked decrease in renal plasma flow; the filtration fraction is consequently reduced.[176, 177] These abnormalities are frequently returned virtually to normal by cortisone.[172, 178] Pitts[10] has postulated, on the basis of acute experiments in adrenalectomized animals, that the effects of cortisone, as well as of desoxycorticosterone, do not represent a primary action of these hormones on renal hemodynamics but depend on the restoration of both volume and composition of body fluids consequent to the re-establishment of electrolyte balance.

The capacity of the kidney to compensate for alterations in acid-base balance is reduced in adrenal insufficiency. This deficit is primarily the result of an impairment of normal base-saving mechanisms that depend on a tubular exchange of hydrogen ions and ammonia for sodium.[12] The administration of cortisone has been demonstrated to cause an increased excretion of ammonia and titratable acidity in response to acid loading, with a resultant conservation of fixed base. It should be pointed out that although the effect of cortisone in the regulation of tubular ion-exchange processes and, secondarily, of renal hemodynamics is similar to that of desoxycorticosterone, much larger doses of the former steroid are required.[179] This is in keeping with the fact, previously emphasized, that cortisone is intrinsically much less active than desoxycorticosterone in the control of electrolyte excretion.

Although the renal abnormality associated with adrenal insufficiency has not been completely defined, there is sufficient evidence that the incapacity to limit salt loss is due to decreased tubular reabsorption of sodium.[157, 180] However, Roemmelt et al.[12] have demonstrated that adrenalectomized animals infused with hypertonic saline solution are unable to excrete the administered salt at a normal rate because of increased tubular reabsorption of sodium. Similarly, Burnett[178] showed that urinary sodium excretion of patients with Addison's disease given 4 per cent sodium chloride solution intravenously was markedly subnormal. Neither a significant rise in urine flow nor an increase in urinary sodium concentration was observed. The defect was partially corrected by cortisone but little influenced by desoxycorticosterone. These studies illustrate an important aspect of cortisone action: its effectiveness in increasing renal capacity to change the reabsorptive rate of sodium irrespective of the initial defect probably reflects a fundamental action directed toward the maintenance of homeostasis. This concept of adrenal steroid function has been well delineated by Ingle.[181]

Normal subjects and patients with intact adrenal glands: The administration of comparatively large doses of cortisone to normal subjects produces definite alterations in renal function. Glomerular filtration rate is significantly elevated; renal plasma flow is usually only slightly increased, and the calculated or effective flow is ordinarily not significantly changed because of an accompanying fall in venous hematocrit.[178, 182] Consequently, the filtration fraction is increased. Since T_mPAH (maximum tubular transfer rate of para-amino hippurate) was not elevated, Burnett et al.[178] concluded that cortisone does not produce an increase in kidney mass. A rise in glomerular hydrostatic pressure could not be implicated as the cause of increased glomerular filtration rate in normal subjects. Although an elevation of blood pressure was observed in patients with Addison's disease, the resultant rise in hydrostatic pressure was insufficient to account for the significant changes in filtration rate.

Studies carried out by Ingbar et al.[182] in normal subjects demonstrated an increased urinary excretion of uric acid and phosphorus after cortisone administration. In both instances the rise in urinary output was independent of changes in serum concentration and the ratio of excreted solute to filtered solute rose markedly. The changes observed indicate an alteration of tubular transport of uric acid and phosphorus under the influence of cortisone. Sodium excretion decreased as a result of increased tubular reabsorption. Potassium output, however, was significantly elevated only during concomitant sodium loading, emphasizing again the potential importance of sodium reabsorption as a conditioning factor in the renal excretion of potassium. That there is a renal component in the glycosuria that may be induced in man by the administration of cortisone has been indicated by Conn et al.,[115] who noted glycosuria associated with little or no rise in blood sugar. It is evident that a decrease in renal threshold may result from a reduction in T_m glucose (maximal tubular transfer rate of glucose), or an increase in tubular load due to either a rise in blood sugar concentration or an elevation of glomerular filtration rate, or a combination of both.[183]

Antopol[184] observed granulomatous nodules in the kidneys of mice given relatively large doses of cortisone, and Selye[185] reported that the administration of large doses of this hormone to unilaterally nephrectomized rats receiving a high-sodium, high-protein diet may result in hyalinization of glomerular capillaries and eventually in nephrosclerosis. Rich[186] demonstrated, in animals given large doses of cortisone, the development of renal lesions that were morphologically similar to the Kimmelstiel–Wilson nodules found in patients with long-standing diabetes mellitus. Although the majority of clinical reports fail to indicate significant changes in con-

junction with cortisone therapy, the possibility remains that long-continued administration of cortisone at a high dosage level will induce renal changes similar to those reported in cases of spontaneous Cushing's syndrome.[187] It is of interest that repeated clinical trials have revealed cortisone to be relatively ineffective in modifying the inflammatory renal lesions of acute glomerulonephritis,[188] disseminated lupus erythematosus and polyarteritis nodosa,[189] although other lesions of the last two disorders may be remarkably benefited. Indeed, aggravation of hypertension and azotemia has been observed with cortisone therapy in patients exhibiting advanced renal disease in association with these syndromes.

(To be continued)

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MEDICAL INTELLIGENCE

CLINICAL APPLICATION OF A SIMPLE QUALITATIVE SERUM ACETONE TEST IN DIABETES MELLITUS

Otto C. Page, M.D.*

PORTLAND, OREGON

SIMPLE methods for the qualitative and roughly quantitative determination of serum acetone have been known for some time.[1] Duncan,[2, 3] particularly, has pointed out the value of these simple tests in the early diagnosis and treatment of diabetic acidosis. Perhaps because of their very simplicity, the tests have failed to gain the wide recognition they deserve. A limited experience with one of these simple tests is herewith reported in the hope that others may be encouraged to use it in situations in which more elaborate determinations are unavailable.

Method

Because of its convenience the nitroprusside method has been found to serve well for the performance of the serum acetone test. This has been carried out either with a commercial preparation (Denco) or a powder that may be prepared in any laboratory, the ingredients being thoroughly mixed and kept dry at all times, as follows: sodium nitroprusside, 1 gm. finely ground; ammonium sulfate, 60 gm.; anhydrous sodium carbonate, 60 gm.

A small amount of powder is deposited on a piece of nonabsorbent white paper, and sufficient plasma or serum added (2 or 3 drops) to saturate the powder. In my experience, the test has correlated better with carbon dioxide content of the plasma when read at three minutes rather than at thirty seconds as usually recommended. A deep-purple color represents a ++++ reaction, and trace to +++ reactions are represented by lesser degrees of lavender and purple. One should not expect the almost purple-black reaction that may result on testing of the urine of patients in severe acidosis. It has been my experience that gross hyperlipemia interferes perceptibly with the rate of the reaction and the depth of color change, and this should be considered in the interpretation of the test. Technicians who have used the procedure for the determination of urine acetone experience no difficulty in interpreting the same test on serum or plasma. For those with little experience with the method, an approximate color chart accompanies the commercial preparation. Dumm and Shipley[4] describe a method for the determination of serum acetone bodies using the nitroprusside powder and serial dilutions of serum with water. They report that results with this method correspond to more accurate quantitative microdeterminations, with an error seldom exceeding 10 mg. per 100 cc. I have found the simple qualitative reaction with whole serum or plasma sufficiently accurate for practical purposes and have no experience with the dilution method.

*Clinical instructor in medicine, University of Oregon Medical School; formerly, fellow in medicine, Joslin Clinic, New England Deaconess Hospital.

Results

When a ++++ serum acetone reaction is found in a patient who has not received treatment for diabetic acidosis, the carbon dioxide content is usually 10 milliequiv. per liter or less. An insufficient number of simultaneous quantitative blood ketone determinations have been performed for accurate correlation, but it is my impression that a ++++ nitroprusside powder reaction in the untreated patient is probably accompanied by a minimum of about 40 mg. per 100 cc. of total ketone bodies in the whole blood. Strict correlation would not be expected since the quantitative method used[5] measures total ketone bodies, including beta-hydroxy-butyric acid, whereas the nitroprusside reagent reacts only with diacetic acid and acetone. A ++ or +++ reaction is usually accompanied by carbon dioxide values between 10 and 20 milliequiv. per liter. A trace or + reaction seems to be accompanied by carbon dioxide values in the normal range or only slightly depressed. With a trace or + reaction the quantitative test for total ketone bodies in the whole blood may be negative.

Development of Diabetic Acidosis

The kidneys handle ketone bodies as nonthreshold substances up to the point where ketone production exceeds their ability to excrete them, and it is not until this point is exceeded that measurable amounts of ketone bodies accumulate in the blood. When ketone-body production does not exceed the ability of the kidneys to clear the blood a "compensated ketosis" may be said to exist, and, although the diabetes is poorly controlled, the danger of diabetic acidosis is not imminent. With the appearance of detectable ketone bodies in the blood a "decompensated ketosis" exists, and the patient is well on the way to clinical diabetic acidosis.

Clinical Applications

Early Diagnosis of "Chemical Coma"

Duncan[2] has stated that the criteria for the diagnosis of "chemical coma" are satisfied by the presence of a ++++ test for sugar and a ++++ test for ketone bodies in the urine and a ++++ test for ketone bodies in the blood, and that these

findings call for immediate administration of 100 units of regular insulin. My results in 25 cases with concurrent carbon dioxide determinations agree with both these conclusions. The patient in Case 23 (Table 1), who had taken her daily maintenance dose of 24 units of regular and 62 units of NPH insulin 4 hours before admission to the hospital, was given 100 units of regular insulin on admission

Table 1. *Data in 26 Cases of Diabetes.*

Case No.	Age	Sex	Initial Blood Values				Insulin Dosage Prior to Admission	Result of Initial Insulin Dose		
			Blood Sugar	Plasma Carbon Dioxide Content	Plasma "Spot" Test	Plasma Acetone		Initial Insulin Dosage	Interval After Insulin	Blood Sugar
	yr.		*mg./100 cc.*	*milliequiv./liter*		*mg./100 cc.*	*units*	*units*	*hr.*	*mg./100 cc.*
1	12	M	740	5	++++	70	100	250	4	163
2	19	M	397	7	++++	88	70	160	2½	175
3	68	F	880	8	++++	81		500		
4	32	F	400	10	++++	63		100	3½	208
5	63	F	920	5	++++	71		400	4	520
6	41	F	300	6	++++		100	140	4½	65
7	27	F	350	9	++++	48		125	3	112
8	17	F	470	6	++++	100		150	3½	185
9	16	F	312	9	+++			50	4	192
10	40	M	407	6	++++		80	60	3	318
11	15	F	403	7	++++		100	100	3½	142
12	15	M	510	12	+++			30 (regular) 30 (NPH)	4	373
13	42	F	585	4	++++			300	4	278
14	24	F	600	9	+++ to ++++			300	5½	187
15	40	M	273	7	++++	65		125	2	111
16	17	F	393	10	++++			100	4	180
17	17	M	410	4	++++	72		130	4	108
18	66	F	397	13	++++			70	2	335
19	67	F	407	13	+++			100	8	160
20	9	F	480	11	+++			50	7	132
21	59	M	430	15	++ to +++	30	80	75	4	65
22	32	F	350	9	0 (uremic acidosis)					
23	15	F	144	7	++++			100	9	76
24	45	F	390	15	+++			60	3	300
25	10	F	550	10	+++			100	8	77
26	19	M	303	6	++++			100	3	198

on the basis of a ++++ blood acetone reaction, despite the fact that the urine showed only a yellow-green reduction with Benedict's solution. Five per cent glucose in water and large amounts of carbohydrate by mouth were started as soon as a blood sugar level of 144 mg. per 100 cc. was reported. There was no untoward reaction, but this case points to the necessity for including a +++ to ++++ test for sugar in the urine as a prerequisite for administration of the initial 100 units of insulin.

Table 2. *Guide to Initial Insulin Dosage.*

Blood Sugar	Dosage of Insulin
mg./100 cc.	*units*
300–400	100–150
400–500	150–200
500–600	200–300
600 plus	300–400

When carbon dioxide determinations are unavailable and the treatment of acidosis is to be conducted on the basis of ++++ test for serum acetone combined with blood sugar determinations, the figures presented in Table 2 serve as a safe approximate guide to the initial insulin dosage in adult patients; 100 units is given on the diagnosis of diabetic "chemical coma," 50 units intravenously and 50 units subcutaneously, and the remainder as soon as the initial blood sugar is reported.

If the patient is semicomatose or comatose, the next higher insulin schedule is indicated. If the patient is young (between ten and fifteen years of age) or the diagnosis has recently been made, the next lower schedule is employed. The initial dose probably should not exceed 200 units in patients who have not received prior insulin treatment.

Under this plan of treatment the blood sugar is determined two and a half or three hours after the first dose of insulin, and usually no more insulin is given until the blood sugar value is available. In deciding upon the insulin dose after the second blood sugar determination, one must remember that in general the larger the dose of insulin, the longer the period before the maximum effect is obtained on the blood sugar level. Thus, with 150 to 200 units of insulin the maximum depression may not be reached for six hours rather than the usually cited three hours for smaller doses of insulin. On the other hand, if the second blood sugar level shows no drop, or has risen above the initial level, resistance may be inferred, and the initial dose of insulin should be repeated or the second dose of insulin should be larger than the first.

In a small number of patients, this schedule will provide more insulin than necessary to bring the blood sugar to within normal range. There is no

danger of hypoglycemic reactions if 10 to 20 gm. of carbohydrate per hour is supplied in case the second blood sugar determination shows an excessive rate of fall. Most patients who show an excessive response have relatively mild acidosis, and the carbohydrate can usually be given by mouth in the form of 100 to 200 cc. of orange juice or ginger ale every hour. However, 5 per cent glucose in water should be started intravenously if the patient is unable to tolerate carbohydrate by mouth.

Detection of Incipient or Early Acidosis

The patient with a ++ to +++ reaction for serum acetone is not critically ill in most cases and is usually an easier problem in management. It is at this point, however, that the patient may be easily brought back to a state of compensated ketosis but may just as readily slip into more severe acidosis if the situation is not appreciated. The patient showing a + test for serum acetone cannot be considered to be in clinical acidosis and probably will exhibit a normal response to insulin. One would be inclined to watch and treat this patient somewhat more carefully than the patient with ketonuria alone, and the patient should certainly be given supplementary insulin by urine test every four to six hours until the glycosuria and ketonuria show signs of clearing.

Differential Diagnosis

Diabetic nephropathy. With greater numbers of young diabetic patients being kept alive for fifteen or more years one can expect to be faced more and more frequently with the necessity for differentiating uremic acidosis complicating diabetic nephropathy and true diabetic ketosis.[6, 7] The treatment differs markedly, depending on the etiology. The patient in true diabetic acidosis needs large doses of insulin, but it has been shown that patients with nephropathy and uremia may be peculiarly sensitive to insulin.[8, 9] The patient with diabetic nephropathy and renal acidosis may fulfill all the usual criteria for the laboratory diagnosis of diabetic acidosis (glycosuria, ketonuria, hyperglycemia and decreased carbon dioxide content) except for the presence of significant amounts of retained acetone bodies in the blood (as in Case 22). Quantitative ketone-body determinations in the blood are usually not available and are not as rapid as the simple quantitative test.

Posthypoglycemic state. One is occasionally confronted with a patient who receives protamine zinc insulin and whose history suggests an insulin reaction but who may show glycosuria, lethargy and ketonuria. Here again the nitroprusside powder test for serum acetone can quickly differentiate the stupor secondary to diabetic acidosis from that which may accompany the posthypoglycemic state.

Nausea, vomiting and abdominal pain. Nausea and vomiting as well as abdominal pain are, in a sense, nonspecific symptoms, common to both diabetic acidosis and various relatively benign and serious intra-abdominal conditions. A ++++ serum acetone reaction, in the absence of definite localizing signs, should further incline one to withhold surgical intervention to see if correction of the acidosis will reverse the symptoms. Diabetic acidosis could be ruled out as the cause of the symptoms if acetone were absent from the serum or only a + to ++ reaction were obtained.

Summary

The technic, interpretation and clinical applications of the simple nitroprusside qualitative test for serum or plasma acetone are re-evaluated. Simultaneous determinations of serum carbon dioxide content and quantitative blood ketone levels in a limited number of cases are discussed.

It is pointed out that the test is not simply a substitute for plasma carbon dioxide determinations, but may yield additional information of aid in the evaluation and treatment of the acutely ill diabetic patient.

2222 N. W. Lovejoy St.

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AMAZONIA: U. S. A. — 1952

THE following verses, emanating from the pen of a professor of medicine in far-away Ioway, are said to have been inspired by an editorial in the *Journal* of November 27, 1952, commenting on the increasing preponderance of females in modern society.

A litany on the decline of the male in our growing matriarchy written after a sullen view of insurance statistics and newspapers.

Insurance figures now attest
Facts which lead to male unrest.
Women have since '45
Kept more of themselves alive;
Man till then was here ascendant
Now he has a place dependent
And with every passing May
Fewer men than women stay
Though more boys get born each day.
The male continues to decline;
Of him die ten, of women nine,
More men than women leave our shores
More men than women die in wars
But war brides like to immigrate
And so the tide does not abate.
We men begin to brood on menaces
A future of parthenogenesis
With women holding all the tenaces.
As if this trend were not a worry
The news sheets spread a stranger flurry
And what I read does most alarm me:
A soldier boy who left our army
Between new hormones and the knife
Is now a girl and may be wife.
Boys will be boys they used to say
But science makes such words passé.
Our sad decline is very rough
Need things get tougher when so tough?
Save men from all such evil stuff
One sex per person's quite enough.

WILLIAM B. BEAN, M.D.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39071

PRESENTATION OF CASE

A sixty-two-year-old man was admitted to the hospital for consideration of gastric surgery.

Four years before admission the patient was found to have pernicious anemia. He was regularly given liver injections in the clinic, which provided excellent control of the anemia, and had an annual gastrointestinal series. Twenty-one months before entry a roentgenogram showed a prominent mucosal fold on the posterior wall high on the lesser curvature (Fig. 1). This was unchanged one year and again four months before admission. Gastroscopy ten months before admission revealed what appeared to be atrophic gastritis and a benign polyp on the anterior wall of the antrum toward the lesser curvature. Because of these persistent findings the patient was referred to the hospital.

He had had no gastrointestinal symptoms and had gained 10 pounds in weight during the past year. There was no history of constipation, abdominal pain or food intolerance.

On physical examination the patient was well developed and well nourished, and did not appear ill. The general examination was completely negative.

The temperature, pulse and respirations were normal. The blood pressure was 158 systolic, 94 diastolic.

The urine was normal. The blood hemoglobin was 14.5 gm. and the white-cell count 7800. The

FIGURE 1.

nonprotein nitrogen was 30 mg., and the total protein 6.3 gm. per 100 cc., and the prothrombin time 15 seconds, (normal, 13 seconds). A gastrointes-

tinal series showed a normal-appearing esophagus. No defects were identified in the stomach, duodenal cap or loop, or the small bowel. The previously questioned polypoid defects in the antral region of the stomach were not confirmed in this examination.

On the fourth hospital day an operation was performed.

Differential Diagnosis

Dr. Grant V. Rodkey*: May we see the x-ray films?

Dr. Stanley M. Wyman: I have tried to select the pertinent films from several examinations. This film is the original observation of the prominent fold described, this being inward projection of the wall of the stomach involving the mucosa apparently. This is seen later on a different type of film as a polypoid structure (Fig. 1). I do not think the discrepancy in location with that described gastroscopically need be taken too seriously since it is hard to be certain of geography in these examinations. The last examination shows a different appearance of the stomach; whether or not this is a valid observation I cannot say. In this sort of situation one really needs to palpate the stomach and thus to determine whether the changes seen are constant — whether or not there is any stiffening of the wall of the stomach. There seems to be, however, some narrowing of the wall of the stomach, and certainly, judging from the films alone, I should be forced to wonder whether there was some process infiltrating the gastric wall; I cannot go any farther than to wonder about it.

Dr. Rodkey: Would you think it was a rather unusual appearance around the body of the stomach?

Dr. Wyman: I think it could be due to underfilling of the stomach, which is lying transversely; however, I should wonder whether the stomach was being constricted. I do not see the fold that we originally saw with any degree of certainty on these later films. I think, however, that it would be quite dangerous to say it was no longer present.

Dr. Rodkey: This case highlights one of the dilemmas in the treatment of cancer of the stomach. The frequent occurrence of gastric cancer and polyps of the stomach in association with pernicious anemia is quite generally recognized. One of the earliest investigators to note this association was Henricus Quincke,[1] who in 1876 observed a patient with pernicious anemia who died of cancer of the stomach. Since that time several autopsy studies have been undertaken to elucidate the relation between carcinoma of the stomach and pernicious anemia. One of the best of the series was a report by Kaplan and Rigler[2] in 1945. Of 23,231 autopsies on patients more than forty-five years of age, they found 293 patients with pernicious anemia; of these 293 cases, 36 showed cancer of the stomach, which the authors estimated to be about three times as common among patients with pernicious anemia as it was in the remaining autopsy population of the same age group. The same group of investigators studied a subgroup of their material, which contained 9 cases of cancer and 7 cases of benign polyps among 146 cases of pernicious anemia.

These pathological studies have been supplemented by statistical analyses of clinical material that show essentially the same findings.* A recent report from Denmark is quite interesting. Jørgensen[3] has studied the mortality in cases of pernicious anemia diagnosed between 1930 and 1942. They were average patients who had about average treatment — neither too good nor too bad. In this series of 206 cases followed for an average period of seven and eight-tenths years, cancer of the stomach was approximately three times as frequent as in a group of similar age, sex and follow-up period without pernicious anemia. In this connection, most of us know of the attempt by Wangensteen[4] to pick out carcinoma of the stomach from certain groups of patients who were known to have the precursors of carcinoma. Table 1 demonstrates some of the results reported in 1951 among three of the groups of conditions that were studied, the achlorhydric, the hypochlorhydric and the pernicious-anemia groups. It is apparent that pernicious anemia was about six times more frequent as a precursor of carcinoma than either of the other two conditions.

Table 1. *Gastric Acidity in Cancer.**

Group	No. of Patients	Patients with Gastric Polyp	Patients With Cancer
		%	%
Achlorhydric	1287	2.4	0.54
Hypochlorhydric	271	1.1	0.36
Pernicious anemia	115	3.4	3.4

*Modified from Wangensteen.[4]

The problem presented by the protocol is twofold: to make the diagnosis and to discuss what should be done about it. The diagnosis of cancer of the stomach rests chiefly on four pillars, the main one of which is the x-ray examination. In a recent series of 344 cases of proved cancer of the stomach reported by Jemerin and Colp,[5] x-ray examination showed cancer of the stomach to be present in 293, or an accuracy of about 85 per cent. This included repeated examinations in some cases. I think most people would agree that this method is least likely to be accurate in patients in whom the disease is very early or in cases in which there is a diffuse involvement of the stomach without gross interference of the gastric outline.

The second most helpful aid is gastroscopy. In the group of 344 cases cited above, gastroscopy was performed on 243 patients, the presence of cancer

*Assistant in surgery, Massachusetts General Hospital.

being confirmed in 194 — or about 80 per cent. Benedict[6] has also recently stressed the importance of gastroscopy and biopsy in making this diagnosis. However, not all the areas of the stomach are equally accessible to the view of the gastroscope; the antrum is a particularly difficult area to visualize.

The third aid in diagnosis, considerably less helpful than the previous two, is the study of the gastric acidity. Although achlorhydria is a constant feature of pernicious anemia, it is not always observed in cases of gastric cancer when pernicious anemia is not present and, therefore, is not too reliable an aid in diagnosis. It is perhaps more reliable as a screening test.

The fourth and newer aid in the diagnosis of gastric cancer — probably more helpful than the previous one — is the study of the gastric cytology. Seybolt, Papanicolaou and Cooper[7] reported a series of 974 cases in which the specimens obtained were satisfactory for examination (the problem of obtaining a satisfactory specimen is important in gastric cytologic studies because of the tendency of the gastric juice to digest the exfoliated cells). In this series of 974 specimens the smears were positive in 50 per cent of cases in which cancer was later demonstrated to be present; in 2.5 per cent the smears were falsely positive. In this hospital Ulfelder et al.[8] reviewed a series of cases of which 45 specimens were satisfactory for cytologic examination; of these, 14 patients were proved at operation to have gastric cancer. Of these 14 cases of proved cancer, the smears were positive in 12. In another recent summary of experience with cytologic smears published by Traut and his associates,[9] malignant cells were found in 30 of 42 cases in which the smear was satisfactory for examination — an incidence of correct finding of 71 per cent. These investigators are using papain in an attempt to dissolve the gastric mucus and facilitate the shedding of cells by tumors of the stomach. This is an interesting idea, but the experience to date with papain has not been extensive enough for one to know whether it will become a routine adjunct to this examination.

Turning from the problem of diagnosis, we face a dilemma in treatment. It would be helpful if, in pernicious anemia, one portion of the stomach showed a marked predisposition to the development of cancer, but this really is not the case. It is true that, in general, most of the atrophy of the mucosa takes place in the fundus and body of the stomach in pernicious anemia, but in a series of 102 cases of cancer associated with pernicious anemia, compiled from several sources,[10, 11] the distribution of the site of the development of cancer was about as follows: the lower third of the stomach, 44 cases, the middle third, 33 cases, the upper third, 18 cases, and diffuse involvement, 7 cases. Of course, given a group of persons who have perhaps three times the normal chance of developing cancer of the stomach, which can arise in any portion of the stomach, the surgeon would be quite happy to be entirely rid of the stomach. Yet, even though the mortality rate of total gastrectomy has become quite reasonable, he does not find that an attractive solution since the operation may have serious sequelae. Marked weight loss is quite common, and patients have been known to die of inanition after total gastrectomy without any evidence of recurrent cancer at postmortem examination.[12] On the other hand, after a subtotal gastrectomy — even when the growth is encompassed by a suitable margin — a segment of stomach is still left behind that is prone to develop a new tumor. That leaves us in quite a dilemma.

The patient under discussion was a male in the age group with the maximum incidence of cancer of the stomach. He had pernicious anemia, which we believe gave him a threefold chance of having cancer of the stomach over other males of the same age group. Although there was no positive evidence of cancer, the repeated x-ray examinations raised some question about the prominence of a mucosal fold, and there was a slight suspicion that the last examination showed an infiltrating growth along the body of the stomach. The gastroscopy was helpful in that a polyp was definitely visualized on the anterior wall of the antrum. That finding is significant because it is generally agreed that polyps of the stomach are precursors of cancer. Finally, there was no mention in this protocol of gastric cytologic examination, which must have been done on several occasions. On the evidence I am given, I shall say that he had an infiltrating carcinoma of the stomach, which, I suppose, involved the middle third — perhaps also the fundus; I suspect that the operation was a total gastrectomy. I should guess that he had metastatic carcinoma of the lymph nodes as well.

DR. JACOB LERMAN: Did you hold back the cytologic examinations?

DR. BENJAMIN CASTLEMAN: No. I do not believe any reports of cytologic smears are in the record.

DR. EDWARD B. BENEDICT: There was one that was doubtful.

A PHYSICIAN: At what stage should one consider a total gastrectomy in patients with pernicious anemia?

DR. RODKEY: That is a hard question. I do not think anybody can answer it. No patient likes to lose a stomach, and no responsible surgeon likes to deprive a patient of his stomach without some cogent indication. I do not think most surgeons would do a prophylactic total gastrectomy; not many would do a prophylactic subtotal gastrectomy. Certainly, these patients ought to be followed carefully by x-ray examinations — as has been done in many clinics — and by cytologic smear. The problem in cancer of the stomach, not only with pernicious anemia but in all cases, is the difficulty of an early diagnosis. All our diagnostic methods, except possibly cytologic smear, are helpful chiefly in cases in which the cancer is advanced. This man,

because he had no symptoms whatever of cancer of the stomach, — unless he did not have it, of course, — typifies the patients we hope to find. By the time symptoms from cancer of the stomach

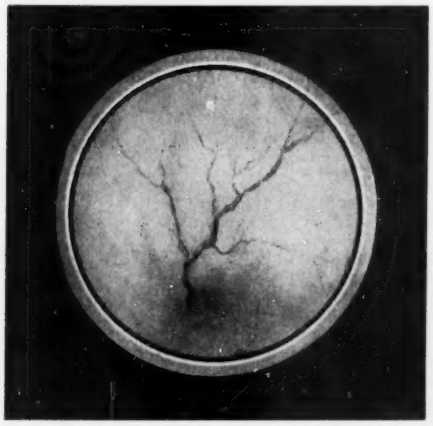

FIGURE 2. *Atrophy of the Gastric Mucosa (Reproduced from Benedict,[13] with the Permission of the Publishers).*

are noticeable, the patient is already far gone. It is only in the early phases, when the only symptom may be slight indigestion (usually treated by sodium bicarbonate or other alkali), that cancer of the stom-

FIGURE 3. *Adenocarcinoma, Grade 1 (Reproduced from Benedict,[13] with the Permission of the Publishers).*

ach is curable. We are all concerned to devise some examination or test that will make an early diagnosis possible.

DR. BENEDICT: This slide (Fig. 2), from a patient whom we saw ten or fifteen years ago, shows the atrophy of the gastric mucosa that is constant in pernicious anemia — marked pallor, absence of rugae, thin mucosa and blood vessels readily visible through the mucosa. That type of mucosa on microscopical examination shows intestinal metaplasia and is a fertile field for the development of carcinoma. Carcinomas do not seem to develop in superficial or hypertrophic gastritis even after many years. The next slide (Fig. 3), from the same patient, demonstrates the development of a polypoid lesion that was quite suggestive of carcinoma and proved to be an adenocarcinoma, Grade 1. This was resected locally, and the patient died within a year of rapidly spreading cancer. The next slide (Fig. 4) pictures the type of lesion — a benign pedunculated polyp — that was present in the patient under discussion. The biopsy from this specimen was reported as showing a benign adenom-

FIGURE 4. *Benign Adenomatous Polyp.*

atous polyp. Although there was no pernicious anemia in this case, everybody was so worried about the possibility of cancer that the polyp was later resected and proved to be benign. The polyp in the case under discussion looked exactly like this polyp; there was not the slightest evidence of the infiltration or rigidity of carcinoma, and we were quite certain that it was a benign adenomatous polyp.

Some years ago Dr. Arthur W. Allen and I[14] looked up a series of adenomatous polyps and noted that about 40 per cent of them were likely to be malignant. Our figure is somewhat higher than those other authors have given — it varied from 15 to 20 per cent.

DR. F. DENNETTE ADAMS: What did Dr. Benedict mean when he spoke of intestinal metaplasia in the stomach?

DR. CASTLEMAN: Very commonly, in pernicious anemia or in other forms of gastritis, the ordinary mucosa of the secreting epithelium of the stomach changes to one of intestinal type with goblet cells. Some pathologists believe that the intestinal metaplasia in pernicious anemia, which is quite common, is one of the factors that leads to carcinoma.

Clinical Diagnoses

Pernicious anemia.
Atrophic gastritis, with gastric polyps.
?Carcinoma of stomach.

Dr. Grant V. Rodkey's Diagnosis

Carcinoma of stomach.

Anatomical Diagnoses

(*Pernicious anemia.*)
Atrophic gastritis, severe, with intestinal metaplasia.
Adenomatous polyp of stomach.

Pathological Discussion

Dr. Castleman: The first operation on this patient was a subtotal resection; we found two polyps corresponding to what was seen through the gastroscope, which were benign adenomatous polyps

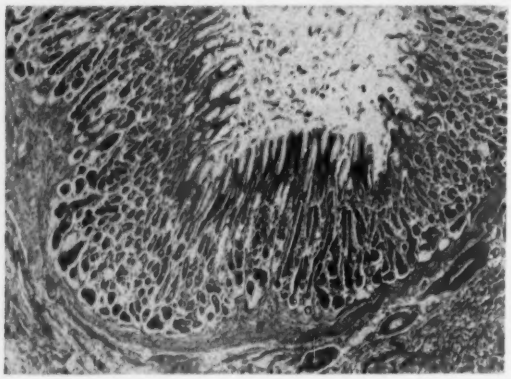

Figure 5.

very similar to the one that Dr. Benedict showed (Fig. 4). However, in addition, we found two small areas of ulceration on the lesser curvature and a very atrophic mucosa throughout the entire stomach. This slide (Fig. 5) is from a normal stomach demonstrating the superficial glands with the secretion, and the glands having the chief and parietal cells; it should be noted how thick this mucosa from the fundus is. In contrast, the next slide (Fig. 6) is from a case of pernicious anemia, one very similar to the one under discussion, in which there was marked atrophy of the mucosa and some intestinal metaplasia. In the next slide (Fig. 7), from the case under discussion, through one of the small areas of mucosal erosion, there is very atrophic mucosa and islands of cells that stain very darkly, some of which are the goblet cells of intestinal metaplasia; a higher magnification through some of these areas (Fig. 8) demonstrates a very active regeneration with any number of mitoses. At first we believed this was adenocarcinoma in situ, but upon further study I decided it was not really cancer but marked regeneration in a severely atrophic mucosa of the type that might well go on to carcinoma. We told the surgeons, who were planning to do a total gastrectomy because of the preliminary report of adenocarcinoma in situ in the two foci of ulcerations, that it was very active regeneration and not cancer. After a great deal of consultation they believed that since the patient was in good condition it would

Figure 6.

still probably be better to do a total gastrectomy. which was done just two days ago. In about a dozen blocks through the resected stomach, we

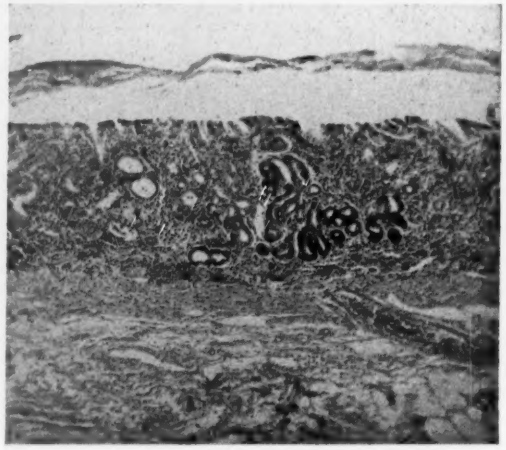

Figure 7.

found areas similar to those which I showed and other areas in which there was early polyposis within the epithelium with large numbers of cystic dilated glands. It reminded me of the cystic endometrial dilatation that we see in hyperplasia of the endometrium, which may also be precancerous. Since the parietal cells that produce the hydrochloric acid were all absent, I wonder how much normal function of this stomach remained. Perhaps such a patient has already been partially adjusted to some of the effects of a total gastrectomy.

DR. BERNARD M. JACOBSON: That is a new and interesting concept of a malfunctioning stomach — it certainly is not clinically true. One did not gather that the patient under discussion had any digestive difficulties or malnutrition or anything of that sort.

I should like to make just one comment. I agree with Dr. Rodkey's excellent discussion of carcinoma of the stomach associated with pernicious anemia. He cited two Scandinavian groups who recently showed that the incidence of carcinoma of the stomach was three times as great in patients with pernicious anemia as among those without pernicious anemia of the same age and sex. Both groups also analyzed their cases by sex and found even more striking figures: in one group the male patients with pernicious anemia demonstrated seven times as great a frequency as patients without pernicious anemia; in the other group there was four times as great a frequency. The female patients, disclosed two and two and a half times as great a frequency, respectively. These data are incomplete in that they are statistics of causes of death of patients with pernicious anemia as stated in death certificates. Even the best figures, such as those of Kaplan and Rigler,[2] were compiled from routine post-mortem examinations of patients with pernicious anemia who died in the hospital. That does not give a true incidence of carcinoma of the stomach associated with pernicious anemia. Theoretically, the true incidence should be determined by follow-up studies of large groups of patients with pernicious anemia for many years who have no symptoms of cancer of the stomach, and in whom it can be found on routine examination.

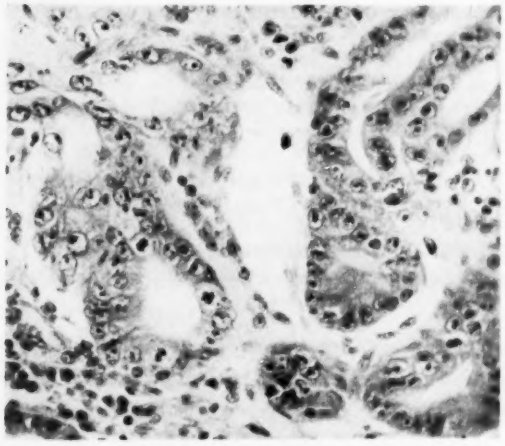

FIGURE 8.

I bear some of the responsibility for the multiple specimens that Dr. Castleman received. I was asked to see this patient before the first operation when the diagnosis was considered to be benign polyp and advised a total gastrectomy. That was radical advice but it was based on certain observations on 2 patients with adenocarcinoma, who later died. Dr. Leland S. McKittrick explored the first patient and did a beautiful, clean resection with an adequate margin; there were no involved lymph nodes. If any patient was considered a good operative risk and a good chance for complete cure that was it. The patient was dead from cancer within a year. The second patient, who was completely asymptomatic but had evidence of cancer of the stomach on x-ray examination, had a subtotal resection; no lymph nodes were involved. Six or seven months later we did another gastric smear, which was positive. The patient went back into the hospital for further resection. There was more cancer in the stomach, either a new cancer or extension of the previous cancer, from which he subsequently died. In the case under discussion, after the initial examination when the benign polyp was found, I was asked again to see the patient and thought that he should have a total gastrectomy. That was before Dr. Castleman told me about the metaplasia.

DR. BENEDICT: Was the first operation a subtotal gastrectomy or a minimal excision?

A PHYSICIAN: A subtotal gastrectomy.

DR. BENEDICT: Followed by a total?

DR. JACOBSON: Yes. It must be remembered that total gastrectomy is not going to have to be considered often. I think it is going to be very difficult to detect carcinoma of the stomach in a patient with pernicious anemia when it is curable at all — once a year, perhaps, in a hospital of this size.

DR. CASTLEMAN: This patient had apparently been adequately treated for four years, and yet his stomach showed a very severe atrophic change — a finding that was recently emphasized in Australia by Motteram,[15] who made a series of gastric biopsies in 43 patients with pernicious anemia and demonstrated that there was no change in the mucosa after treatment.

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The New England Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY

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MICROFILM volumes available to regular subscribers through University Microfilms, 313 N. First Street, Ann Arbor, Michigan.

MATERIAL, other than original articles, should be received not later than noon on Thursday, three weeks before date of publication.

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COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

NINE POINTS FOR AMERICAN MEDICINE

WITH a new year and the changes in leadership that 1953 promised, it was natural that new programs, restatements of former goals, and resolutions to carry them out should have been forthcoming. Stating the objectives of American medicine for 1953, a new president — not, in the interpretation of North Dearborn Street, Chicago, some prospective replacement in Washington or even the retiring head of Harvard University, but Dr. Louis H. Bauer, of the American Medical Association — outlined a program that spokesmen for the medical profession have drawn up for "the preservation of our American system of medicine." The nine points presented by Dr. Bauer do not by any means imply preservation of the *status quo;* they represent a proposal, temperate in language and lofty in principle, to meet the ever-present and growing challenge inherent in the distribution and quality of the medical care available to the American people.

The major objectives for 1953 are enunciated as follows:

1. Work with rural communities to establish facilities for physicians so that we shall have a better distribution of physicians.
2. See that good medical care for the indigent is available everywhere, just as it is in some states.
3. Extend public health coverage to areas lacking it.
4. Develop plans for the care of the chronic invalid.
5. Expand our voluntary insurance program, not only to cover more persons, but to cover those over age 65 and those suffering from illness of long duration.
6. Clean our own house, by disciplining those physicians who are tarnishing the reputation of the whole profession by their unethical acts of over-charging, accepting kickbacks, and making commercial arrangements with pharmacists.
7. See that the public is protected so that they can always obtain the services of physicians.
8. Revitalize our county societies and make them leaders in their communities in all health matters.
9. Inculcate the newly trained physicians in the tradition and ethics of medicine.

To carry out such a program, Dr. Bauer acknowledged, certain changes in present legislation would be imperative. Thus, it would be necessary to establish a department or independent agency of health in the Government (not one tied in with education or social security). The Social Security Act would have to be modified to include the problem of the totally disabled. The present somewhat haphazard system of selecting physicians for the armed forces would have to be revised to ensure that injustices were eliminated and civilian medical programs were not interrupted. It was believed that the problems of the Veterans Administration could be solved without additional legislation.

There can be no quarrel with these objectives or with the steps proposed to fulfill them. The nine points imply recognition (in realistic terms) of the fundamental premise of the report made by the Commission on the Health Needs of the Nation, that "access to the means for the attainment and preservation of health is a basic human right." And neither the patient's right to choose his physician nor the doctor's privilege of unfettered practice

would be interfered with. Not only sincere believers in the validity of the leadership of American medicine but also those, within the profession and outside it, who have hitherto been critical of its performance and doubtful of its motive will applaud this frank acknowledgment that much improvement in American medical care is necessary and capable of attainment. Perhaps, with a new spirit of co-operation and help without compulsion or dictation on the one hand and a sense of humility and willingness to go forward on the other, the Government and the medical profession can work together to give to the American people the best available medical care. Failure to attain that noble goal is not possible in an atmosphere of mutual trust and respect.

HELPING THE DRUG ADDICT

The permanent Central Opium Board of the United Nations has reported recently that the number of narcotic drugs had almost doubled in the last five years, pointing out with some concern an ever wider use of synthetic narcotics without any significant fall in the use of chemical derivatives of opium. This announcement calls to mind a report prepared by the Committee on Drug Addiction and Narcotics of the National Research Council.* Such a report was stimulated by the results of a random sampling of physicians in which the physicians themselves indicated an appreciation of further information on the subject. The federal regulations are reviewed in this report, and a summary of the diagnostic features of drug addiction is given.

Two general principles are emphasized for the guidance of every physician: first that ambulatory treatment of addiction should never be attempted, since institutional treatment is always required; and secondly that narcotic drugs should never be given to an addict for self-administration. The symptoms of abstinence vary considerably from person to person, and there is often variation between those due to opiates and those that result from the synthetic analgesics. Whether the addiction is thought to be due to opium derivatives, the newer chemical sedatives, marihuana or cocaine derivatives, it is well for the physician to seek consultation for confirmation of the diagnosis.

Arrangements for early institutional care are imperative. If local facilities are not available or are not adequate, there are two federal hospitals to which addicts may be admitted. It is possible that special arrangements will need to be made for the adolescent victim of these drugs. The problem of patients with an incurable, fatal disease and suffering much pain is an entirely different one and can be handled by the individual personal physician in charge of the patient.

Legal measures are needed to compel many addicts to go to an institution and to remain there until treatment is completed, and most of the states do not have legislation of this sort. Since it is not necessary for the physician to report addicts to federal or state agencies the size of the problem is not really known. Furthermore, follow-up study of the addict discharged from an institution is often neglected, although it is imperative if he is to be kept in the right path.

The physician will do well to bear in mind the possibility of addiction to the new chemical pain killers and the manifestations of addiction or of forced abstinence. State legislation committing narcotic addicts to institutions until maximum benefits are reached deserves encouragement and support as an objective of modern preventive medicine.

*Council on Pharmacy and Chemistry. What to do with drug addict. *J. A. M. A.* 149:1220-1223, 1952.

HEART FUND — 1953

February, in America, is heart month. Not only does it contain within its abbreviated list of days those that commemorate each year the births of two of the country's greatest-hearted citizens, but sandwiched between them the day immemorially associated with that patron of all well compensated cardiacs, Saint Valentine.

It seems altogether appropriate, then, that February should be set aside for the annual Heart Fund Drive of the American Heart Association, reaching its crescendo on Valentine's Day, February 14. During these twenty-eight days a nationwide goal of 10,000,000 hypertrophied dollars is to be attained, with the trifling sum of $450,000 to be derived from Massachusetts.

Each dollar received is to be divided, like omnis Gallia, although less equally, into three parts. Sixty cents will remain in the local Heart Chapter treasury; 25 cents will go to the American Heart Association, which will allocate half this amount to the support of scientific research; 15 cents will go to the Massachusetts Heart Association to be expended on scientific research and program development.

Recognizing the criticisms that have been made of campaigns for funds outside United Community Services, the Heart Fund offers the following comparisons:

> Community chests were organized to raise money to help meet the health and welfare needs of deserving members of a community.
>
> The Heart Fund was organized to raise money to fight heart disease through scientific research, education and community service. There is no ceiling on the amount of money needed to carry on research because innumerable, hopeful lines are waiting to be explored as soon as funds are available.
>
> Community chests cannot afford to jeopardize the success of their annual appeals by setting goals high enough to meet the minimum needs of Heart Research.
>
> However, the Heart Fund welcomes consideration of a joint campaign with other health agencies dedicated to the attack on specific diseases. Such a campaign would preserve the right of the individual to designate his voluntary gift to the agency of his choice.

The public is urged to give and give generously, but it must be borne in mind that the average citizen will not give so substantially to any single fund, such as that of United Community Services, if he intends also to support other charitable enterprises. Greater demands are being made on the same charity dollar, and each truly charitable organization must recognize the rights of all others when it makes its own appeal.

"THE URBAN SPRAWL"

A DILEMMA that can scarcely be appreciated in this country, with its great areas of unused land, is confronting the British Ministry of Housing and Local Government. Under the title "The Urban Sprawl," the *British Medical Journal* commented editorially in the issue of November 22, 1952, on the Ministry's recent handbook, *The Density of Residential Areas*.

An endless process has apparently been started as the cores of the larger towns decay, of "decanting" the inhabitants into newly developed suburban areas or into the so-called New Towns. It is the using up of fertile land that causes great anxiety; the dilemma is occasioned by the relative social and economic merits of building houses as opposed to flats, and the optimum density of houses or rooms per acre.

In contrast to these real insular problems are the appalling speed and the grim efficiency with which in this country square miles of fertile countryside are converted almost overnight into great prefabricated residential cities.

EVA D. LOTHER

THE *Journal* pays tribute to the memory of Eva D. Lother, who died suddenly on January 30. Her unfailing graciousness and her kindly disposition will long be remembered in the editorial offices, where she had been a devoted worker for twenty-seven years.

The ship Ticonderoga, from Liverpool for Australia, put into Port Philip Bay on the 3d of November, with 200 passengers sick of the cholera. 120 passengers had been previously buried at sea.

Boston M. & S. J., *February 16, 1853*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

AMESBURY — Ivon C. R. Amesbury, M.D., of Boston, died on January 12. He was in his eighty-fourth year.

Dr. Amesbury received his degree from Boston University School of Medicine in 1890. He is survived by his widow.

BABCOCK — Harold L. Babcock, M.D., of Dedham, died on January 21. He was in his sixty-seventh year.

Dr. Babcock received his degree from Boston University School of Medicine in 1910. He was formerly chief surgeon in otolaryngology at Massachusetts Memorial Hospitals and professor of otology at Boston University School of Medicine and a member of the staffs of Choate Memorial Hospital, Woburn, Faulkner Hospital and Cambridge City Hospital, and was a fellow of the American College of Surgeons and the American Medical Association.

He is survived by his widow, a son and two sisters.

CARNEY — Patrick J. Carney, M.D., of Worcester, died on January 9. He was in his seventy-seventh year.

Dr. Carney received his degree from Georgetown University School of Medicine in 1904. He was formerly house physician and team physician at Holy Cross College, and was an associate fellow of the American Medical Association.

He is survived by his widow, two sons and a daughter.

DUCHARME — Alphonse N. Ducharme, M.D., of Shrewsbury, died on December 30, 1952. He was in his seventy-second year.

Dr. Ducharme received his degree from Tufts College Medical School in 1910. He was formerly a member of the staff of St. Vincent Hospital, Worcester, and was a member of the New England Obstetrical and Gynecological Society and a fellow of the American Medical Association.

He is survived by his widow, three daughters, four brothers, four sisters and seven grandchildren.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

EXAMINATIONS IN PREVENTIVE MEDICINE

The next examinations for qualification by the American Board of Preventive Medicine will be held at five places on April 23, 24 and 25, and at the time of the annual meeting of the American Public Health Association in New York City on November 7, 8 and 9, 1953. The April examinations will be held at the following Schools of Public Health: University of California, Berkeley; Harvard University, Boston; Johns Hopkins University, Baltimore; University of Minnesota, Minneapolis; and Tulane University, New Orleans.

Candidates wishing to take the examinations should communicate with the Secretary, Ernest L. Stebbins, M.D., 615 North Wolfe Street, Baltimore 5, Maryland.

BOOK REVIEW

An Inventory of Social and Economic Research in Health. 8°, paper, 197 pp. New York: Health Information Foundation, 1952. $1.50.

The Health Information Foundation, supported by the pharmaceutical, chemical and allied industries, has made available pertinent knowledge of investigations, both published and unpublished, catalogued in various libraries and archives, concerning sociologic and economic health problems. Projects relating to biologic or technical medical developments or mental-health studies are not included. The survey was made in 1951. The book is fully indexed and should prove useful to librarians, social workers and others.

HENRY R. VIETS, M.D.

NOTICES

CUTTER LECTURE

The Harvard School of Public Health announces that the Cutter Lecture on Preventive Medicine, initiated in 1912, will be held in the amphitheater of Building D, Harvard Medical School, on Wednesday, March 25, at 5 p.m. Professor A. Bradford Hill, professor of medical statistics, London School of Hygiene and Tropical Medicine, and honorary director of the Statistical Research Unit of the Medical Research Council, will speak on the subject "Observation and Experiment." The medical profession, medical and public-health students and others interested are cordially invited to attend.

SOUTH END MEDICAL CLUB

A regular monthly meeting of the South End Medical Club will be held at 554 Columbus Avenue, Boston, on Tuesday, March 17, at 12 noon.

Franz J. Ingelfinger, M.D., associate professor of medicine, Boston University School of Medicine, and chief, gastrointestinal Division, Out Patient Department, Massachusetts Memorial Hospitals, will speak on the subject "Biliary-Tract Disease."

All physicians are cordially invited to attend.

BOSTON LYING-IN HOSPITAL POSTGRADUATE COURSE IN OBSTETRICS AND PEDIATRICS

On April 16, 17 and 18 the Boston Lying-in Hospital, in conjunction with the Children's Hospital and with the cooperation of the Massachusetts Department of Public Health, will give a course in obstetrics and pediatrics. This course is designed to acquaint New England physicians with recent advances in the care of the pregnant patient, of newborn infants and of those in the first months of life. It will follow the general pattern of the course offered in 1952.

Analgesia, anesthesia, all aspects of obstetric hemorrhage, erythroblastosis, hematologic diseases of the newborn and infant and other pediatric subjects will be stressed. These and associated subjects will be presented in an intensive and compact two-and-a-half-day program of lectures, conferences, clinical demonstrations, ward rounds and clinicopathological conferences.

The complete program will shortly be published. Further information may be obtained from Dr. Crawford H. Hinman, 221 Longwood Avenue, Boston 15, Massachusetts.

GRADUATE CLUB OF BOSTON, PHI DELTA EPSILON MEDICAL FRATERNITY

A meeting of the Boston Graduate Club of the Phi Delta Epsilon Medical Fraternity will be held at the Boston Club on Wednesday, February 25. This meeting is to be a combined meeting with the Women's Auxiliary, at which the retiring president of the Women's Auxiliary, Mrs. David B. Stearns, and the incoming president, Mrs. David Weintraub, will be guests of honor.

The speaker of the evening will be Judge Jennie Loitman Barron. Cocktails will be served at 6:30, and dinner at 7:30 p.m.

The March meeting will be held at the Boston Club on Wednesday, March 25. The speaker of the evening will be Dr. Richard Ford, Medical Examiner. This is a meeting for undergraduate and graduate members only.

The April meeting, consisting of the annual dinner-dance and initiation for the New England District, will be held on April 25, in the Dorothy Quincy Suite, John Hancock Building. Further details of this meeting will be announced later.

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

A regular meeting of the New England Society of Physical Medicine will be held in the Cheever Amphitheater, Dowling Building, Boston City Hospital, Boston, on Wednesday, February 18, at 8 p.m. (there will be a Council Meeting at 7:30). A symposium on hand injuries will be presented.

PROGRAM

Wounds of the Hand. J. Edward Flynn, M.D.
Tendon Injuries of the Hand. John Crandon, M.D.
Peripheral-Nerve Injuries of the Upper Extremities. William F. Flynn, M.D.
Vascular Problems in Traumatic Hand. John Byrne, M.D.
Fractures of the Hand. Charles Bradford, M.D.

Physicians, rehabilitation personnel and students are cordially invited.

BOSTON SOCIETY OF BIOLOGISTS

A meeting of the Boston Society of Biologists will be held in Lecture Hall B, Allston Burr Hall, Harvard University, Cambridge (opposite the firehouse on Quincy Street between Cambridge and Broadway), on Monday, February 16, at 8 p.m. A symposium on the subject "Is There a Scientific Approach to Human Behavior?" will be presented, with Dr. S. S. Stevens, Harvard University, as chairman. Dr. Mark D. Altschule, Harvard University, Dr. Lawrence S. Kubie, Psychoanalytical Institute, New York City, Dr. B. F. Skinner, Harvard University, and Dr. Norbert Wiener,

Massachusetts Institute of Technology, will participate in the symposium, which will be followed by a discussion.

Announcements of programs for the remainder of the season will be sent to all who request them. Those who wish to support the Society may contribute $1. Suggestions of papers for future meetings are welcome. Inquiries should be directed to Bert L. Vallee, Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts.

NEW ENGLAND CARDIOVASCULAR SOCIETY

A meeting of the New England Cardiovascular Society will be presented by the Massachusetts Memorial Hospitals and the Children's Medical Center in the Dorothy Quincy Suite of the John Hancock Hall, 180 Berkeley Street, Boston, on Monday, March 2, at 8 p.m.

PROGRAM

Massachusetts Memorial Hospitals (Dr. Robert W. Wilkins presiding):

Mechanisms of Production of the Anginal Syndrome by Hypotensive Drugs Currently in Use. Drs. Walter E. Judson and William Hollander.

Effects of Esophageal Dilatation in Patients with Angina Pectoris. Drs. William Hollander, Walter E. Judson and Philip Kramer.

Treatment of Angina Pectoris in Hypertensive Patients. Drs. Dera Kinsey, George P. Whitelaw and Reginald H. Smithwick.

Children's Medical Center (Dr. Benedict F. Massell presiding):

Surgical Closure of Defects of Atrial Septum — Physiologic Considerations. Drs. Walter T. Goodale, Alexander S. Nadas and Roger B. Hickler; Operative Technic. Elton Watkins, M.D.

Intracardiac Left-to-Right Shunt with Moderate Pulmonic Stenosis. Drs. Abraham M. Rudolph, Alexander S. Nadas, Walter T. Goodale and Harold D. Rosenbaum.

Kidney Function in Congestive Heart Failure. Dr. Jack Metcoff.

Free parking privileges are available on St. James Avenue above Clarendon Street (no attendant on duty). Emergency telephone numbers: DEcatur 8-9081 and DEcatur 8-9296.

Interested physicians, medical students, and members of the New England Postgraduate Assembly are cordially invited to attend.

NEW YORK ACADEMY OF SCIENCES

A Conference on Nutritional Factors and Liver Diseases will be held at the Barbizon-Plaza Hotel, New York City, under the auspices of the New York Academy of Sciences on February 13 and 14. Attendance is limited to those invited to participate in the conference and to members of the Academy.

AMERICAN ASSOCIATION OF THE HISTORY OF MEDICINE

The annual meeting of the American Association of the History of Medicine will be held at Columbus, Ohio, in conjunction with the sesquicentennial celebration of that state on Friday, Saturday and Sunday, April 10, 11 and 12. Dr. Linden F. Edwards, of the Department of Anatomy, Ohio State University College of Medicine, Ohio, is chairman of the Program and Arrangements Committee. All interested persons are invited to attend.

NATIONAL INDUSTRIAL HEALTH CONFERENCE

The 1953 National Industrial Health Conference will be held in Los Angeles April 19-24. Professional groups participating in the conference will include the American Conference of Government Industrial Hygienists, United States Navy Industrial Health Organization, American Association of Industrial Dentists, American Industrial Hygiene Association, Industrial Medical Association and American Association of Industrial Nurses.

SOCIETY MEETINGS AND CONFERENCES

FEBRUARY 13 AND 14. New York Academy of Sciences. Notice above.

FEBRUARY 13–28. Springfield Hospital Educational Program. Page 164, issue of January 22.

FEBRUARY 13–MARCH 27. Combined Anesthesia Teaching Conferences of Boston. Page 210, issue of January 29.

FEBRUARY 16. Boston Society of Biologists. Page 307.

FEBRUARY 16–APRIL 20. Hartford Medical Society. Page 42, issue of January 1.

FEBRUARY 17. South End Medical Club. Page 164, issue of January 22.

FEBRUARY 18. New England Society of Physical Medicine. Page 307.

FEBRUARY 18–APRIL 1. Postgraduate Medical Institute Course in General Medicine. Burbank Hospital, Fitchburg. Page 1049, issue of December 25.

FEBRUARY 18–APRIL 8. Postgraduate Medical Institute. Boston. Page 452, issue of September 18.

FEBRUARY 20. New England Center Hospital House Officers' Association. Page 124, issue of January 15.

FEBRUARY 23 AND 24. American College of Surgeons. Page 42, issue of January 1.

FEBRUARY 23–MARCH 23. Postgraduate Course in General Medicine. Cushing Veterans Administration Hospital, Framingham. Page 697, issue of October 30.

FEBRUARY 25. Graduate Club of Boston, Phi Delta Epsilon Medical Fraternity. Page 307.

MARCH 2. New England Cardiovascular Society. Notice above.

MARCH 2–5. Sectional Meeting of American College of Surgeons. Hotel Statler, Boston.

MARCH 2–5. New Orleans Graduate Medical Assembly. Page 828, issue of November 20.

MARCH 2– MAY 4. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 540, issue of October 2.

MARCH 4. Massachusetts School Physicians' Association. Page 266, issue of February 5.

MARCH 8–10. Alumni Postgraduate Convention. College of Medical Evangelists. Page 266, issue of February 5.

MARCH 17. South End Medical Club. Page 307.

MARCH 25. Cutter Lecture. Page 307.

MARCH 25. Graduate Club of Boston, Phi Delta Epsilon Medical Fraternity. Page 307.

APRIL 3. New England Society of Anesthesiologists. Page 418, issue of September 11.

APRIL 10–12. American Association of the History of Medicine. Notice above.

APRIL 15. Massachusetts Academy of General Practice. Spring Clinical Assembly. Hotel Shelton, Boston.

APRIL 16–18. Boston Lying-in Hospital Postgraduate Course in Obstetrics and Pediatrics. Page 307.

APRIL 19–24. National Industrial Health Conference. Notice above.

APRIL 25. Graduate Club of Boston, Phi Delta Epsilon Fraternity. Page 307.

APRIL 29 AND OCTOBER 28. New England Obstetrical and Gynecological Society. Page 868, issue of November 27.

MAY 19–21. Massachusetts Medical Society. Hotel Statler, Boston.

MAY 25–31. First World Congress on Fertility and Sterility. Page 1001, issue of December 18.

DISTRICT MEDICAL SOCIETIES

ESSEX NORTH

MAY 13. Andover Country Club, Shawsheen.

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FEBRUARY 23–MARCH 23. Postgraduate Course in General Medicine. Cushing Veterans Administration Hospital, Framingham.

NORFOLK

FEBRUARY 24.

MARCH 24.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, FEBRUARY 19

THURSDAY, FEBRUARY 19

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*12:00 m.–1:00 p.m. Current Concepts of Pancreatic Surgery. Dr. Kenneth Warren. Stearns Auditorium, New England Center Hospital.

*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, FEBRUARY 20

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

*10:00 a.m.–1:00 p.m. Medical and Surgical Grand Rounds. Dr. George W. Thorn and Dr. Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

10:30–11:15 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.

*10:30 a.m.–1:30 p.m. Combined Medical and Surgical Rounds. Stearns Auditorium, New England Center Hospital.

(Notices concluded on page xiii)

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(*Additional advertisements on page xii*)

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NOTICES (*Concluded from page 308*)

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.
*7:00 p.m. Some Contributions to the Physiology of Gastric Secretions and the Peptic Ulcer Problem. Dr. Lester R. Dragstedt. New England Center Hospital House Officers' Association. Stearns Auditorium, New England Center Hospital.
*7:00–9:00 p.m. Combined Anesthesia Teaching Conference of Boston. Amphitheater, Evans Memorial, Massachusetts Memorial Hospitals, Eighth Floor, 65 East Newton Street.

SATURDAY, FEBRUARY 21

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.
*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

TUESDAY, FEBRUARY 24

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
11:00 a.m.–12:00 m. Regular Grand Rounds of the Pediatric Department. Dowling Amphitheater, Boston City Hospital.
12:00 m.–1:00 p.m. Tumor Clinic. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.
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WEDNESDAY, FEBRUARY 25

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Medical Conference. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.
*12:00 m.–1:00 p.m. Metabolism Conference. Dr. Schwartz. Stearns Auditorium, New England Center Hospital.
12:30 p.m. Weekly Pathological Meeting. Joslin Amphitheater, New England Deaconess Hospital.
*4:00 p.m. Thoracic Conference. Held by Overholt Clinic. Harris Hall, New England Deaconess Hospital.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Neuropathology Conference. Drs. Adams and MacMahon. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
6:30 p.m. Graduate Club of Boston, Phi Delta Epsilon Medical Fraternity. Boston Club.
*7:30 p.m. Lahey Clinic Lectures. Basic Mechanisms of the Anemias and Deficiency Anemias. Dr. Donat P. Cyr. Hemolytic Anemias, Dr. John W. Norcross. Joslin Auditorium, New England Deaconess Hospital.

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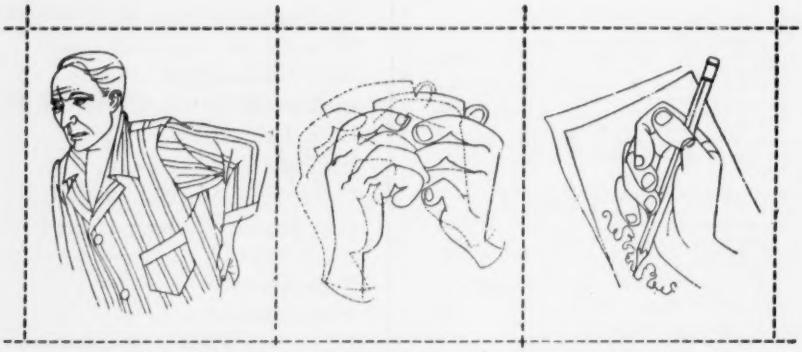

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